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Cognitive ageing and late-life depression across cultures

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Cognitive ageing and late-life depression across cultures

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Thesis submitted for the degree of Doctor of Philosophy
in Health Service and Population Research

King's College London, Institute of Psychiatry, Psychology and Neuroscience

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ABSTRACT

This thesis examined the role of education and depression symptoms to late-life cognitive inequalities. The inquiry was conducted in several stages.

The first line of investigation examined whether a more highly educated recently born cohort had higher levels of cognitive performance and slower rates of cognitive decline in late life compared to a less highly educated earlier born cohort of the same age (65 to 75 years old at baseline). Data were used from the Longitudinal Ageing Study Amsterdam (LASA). Findings from Linear Mixed Models suggest that the later born cohort had higher baseline levels of processing speed, inductive reasoning and general cognitive performance, but showed similar or steeper rates of cognitive decline compared to the earlier born cohort. Education duration accounted for cohort differences in baseline levels of inductive reasoning and general cognitive performance, but it did not account for cohort differences in cognitive decline over 6 years of follow-up.

The second line of research examined which symptom dimensions of depression may show stronger associations with cognitive dysfunctions in late life. This research question was addressed in two separate psychometric studies, one conducted among older adults in Latin American countries (10/66 study) and the other conducted among older adults in the Netherlands (LASA study). Multiple Indicators Multiple Causes Models were used to examine cross-sectional associations between cognitive abilities and latent depression dimensions in the context of adjustment for differences in item response behaviour due to country of residence,

age, gender and cognitive function levels. Findings from the 10/66 study suggest that poorer delayed recall performance was related to higher affective suffering symptoms and higher motivational symptoms. Motivational symptoms had a stronger negative association with verbal fluency performance than affective suffering symptoms. In both studies item response biases were of small magnitude and did not affect substantive conclusions.

The third line of investigation informs on the longitudinal direction of influence and timing of the association between cognitive abilities and depression symptoms (conceptualized as a unitary construct and as specific symptom dimensions). This inquiry was conducted in two separate studies: the 10/66 study with a follow-up duration of 3 years (using cross-lagged path analyses), and the LASA study with a follow-up duration of 13 years (using cross-domain latent growth curve models). Findings from the 10/66 study suggest that most prospective associations between cognitive abilities (i.e., verbal fluency, immediate recall and delayed recall) and overall depression symptoms / specific symptom-dimensions were bidirectional. Baseline motivational symptoms of depression were not related to follow-up verbal fluency performance, whereas baseline delayed recall performance was not related to follow-up affective suffering levels. Findings from the LASA study suggest that poor initial memory performance predicted an increase in overall depression symptoms and a specific increase in depressed affect over time, whereas processing speed decline was accompanied by an increase in overall depression symptoms and a specific increase in somatic symptoms.

In conclusion, findings from this thesis suggest that education alone has a

limited role in accounting for cohort differences in cognitive ageing. The interplay between depression and cognitive functioning is complex. Whether depression co-occurs, precedes, accompanies, or follows cognitive dysfunctions may depend on the depression symptom dimensions experienced and on the timing of the assessments.

STATEMENT OF AUTHORSHIP

The research investigations conducted for this thesis were based on secondary data analysis using the 10/66 Dementia Research dataset in six Latin American countries and the Longitudinal Aging Study Amsterdam dataset in the Netherlands. On commencing my PhD data were already collected. I am grateful to the participating individuals and to the primary investigators for providing me with access to these datasets.

The work presented in this thesis is original and my own work. I formulated the research questions, planned and conducted the analyses, as well as interpreted the findings, and wrote the first draft of all the chapters and papers. Furthermore, I managed the peer review process, with guidance and inputs from supervisors and collaborators.

The studies presented in Chapter 5 and Chapter 7 are based on data from the 10/66 Dementia Research Group. This work was conducted under the guidance of my supervisors: Prof. Martin Prince and Dr. Matthew Prina..

The studies presented in Chapter 3, Chapter 4 and Chapter 6 are based on data from the Longitudinal Aging Study Amsterdam. This work was conducted under the guidance of my supervisors and collaborators: Prof. Martin Prince, Dr. Matthew Prina, Prof. Dorly Deeg, Prof. Aartjan Beekman, Dr. Martijn Huisman, Dr. Hannie Comijs, Dr. Marja Aartsen and Dr Graciela Muniz.

PUBLICATIONS

Chapter 3 is based on the following journal publication:

Brailean, A., Huisman, M., Prince, M., Prina, A. M., Deeg, D. J. H., & Comijs, H. (2016). Cohort Differences in Cognitive Aging in the Longitudinal Aging Study Amsterdam. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences.*, Advance online publication. doi:10.1093/geronb/gbw129

Chapter 4 is based on the following journal publication:

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
AD	Alzheimer's Disease
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CES-D	Center for Epidemiologic Studies Depression Scale
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CI	Confidence Interval
CVA	Cerebrovascular accident
DIF	Differential Item Functioning
DSM	Diagnostic and Statistical Manual of Mental Disorders
GDS	Geriatric Depression Scale
GMS	Geriatric Mental State
HIC	High income countries
LASA	Longitudinal Aging Study Amsterdam
LGCM	Latent Growth Curve Models
LMIC	Low and middle income countries
MAR	Missing at random
MCAR	Missing completely at random
ML	Maximum likelihood
MLR	Maximum likelihood robust
MNAR	Missing not at random
MMSE	Mini Mental State Examination
MCI	Mild cognitive impairment
MDD	Major Depressive Disorder
MIMIC	Multiple Indicators Multiple Causes
OR	Odds ratio
PCA	Principal Components Analysis
RCPM	Raven Colored Progressive Matrices

RMSEA	Root Mean Square Error of Approximation
SEM	Structural Equation Modelling
TLI	Tucker Lewis Index
WLSMV	Weighted Least Squares Mean and Variance-Adjusted

CHAPTER 1. BACKGROUND

1.1 Introduction

A major challenge that countries worldwide are currently facing is population ageing. Declining fertility and increasing life expectancy have led to an increase in the number and proportion of older adults in the general population (United Nations, 2013). Population ageing is expected to lead to a dramatic increase in the prevalence of ageing-related health problems such as cognitive impairment and dementia. Dementia is anticipated to bring about high economic and public health burden worldwide (Wimo et al., 2016; Wimo et al., 2013). The burden is expected to be higher in low and middle income countries (LMIC) where demographic ageing is proceeding more rapidly than in high income countries (HIC) (Prince et al., 2009). In the absence of curative treatment for dementia the emphasis is on modifiable factors that could maintain cognitive health, slow down cognitive decline and delay the onset of dementia.

The concept of cognitive reserve provides one possible explanation for the frequently reported finding that individuals with greater educational and occupational attainment and those more cognitively active are able to sustain higher levels of neuropathological burden before manifesting cognitive deficits (Stern, 2002). Educational attainment is the most frequently used proxy measure for cognitive reserve (Opdebeeck, Martyr, & Clare, 2016). Meta-analytic evidence suggests that higher educational attainment predicts better cognitive performance, as well as lower rates of dementia and MCI (Caamano-Isorna, Corral, Montes-Martinez, & Takkouche, 2006; Luck, Lupp, Briel, & Riedel-Heller, 2010; Opdebeeck et al., 2016). Factors such as education, occupational complexity, and participation in

cognitively stimulating activities contribute towards building cognitive reserve at different life stages and they have been shown to have both individual and combined effects on cognitive outcomes in late life (Opdebeeck et al., 2016).

Over the past century cognitive test scores have increased across generations, a finding known as the “Flynn effect” (Flynn, 1987). Most studies suggest that later born cohorts have better levels of cognitive performance in late-life compared to earlier born cohorts of the same age, but it is not clear whether later born cohorts also show slower ageing-related cognitive decline (Dodge, Zhu, Lee, Chang, & Ganguli, 2014; Finkel, Reynolds, McArdle, & Pedersen, 2007; Gerstorf, Ram, Hoppmann, Willis, & Schaie, 2011). It has been theorised that cohort differences in cognitive functioning in late-life may be explained by higher educational attainment in more recently born cohorts. There is currently insufficient evidence to determine the extent to which educational attainment explains cohort differences in levels and trajectories of cognitive performance in late life. Understanding the factors associated with improvements in cognitive performance across birth cohorts has implications for extending the window of healthy ageing. Due to better cognitive reserve (built through schooling), later born cohorts may not spend more years of life in poor cognitive health despite having higher life expectancy than earlier born cohorts (Skirbekk, Stonawski, Bonsang, & Staudinger, 2013).

Depression is one of the factors that may worsen cognitive functioning in old age, through various mechanisms including lowering cognitive reserve (Butters et al., 2008). Although depression frequently co-occurs with cognitive dysfunctions

in late life, the nature, timing and direction of the association is unclear. There is still debate on whether depression is a risk factor for cognitive impairment, a psychological reaction to perceived cognitive dysfunctions, or a prodromal syndrome of dementia (Ownby, Crocco, Acevedo, John, & Loewenstein, 2006; Prince et al., 2014; van den Kommer et al., 2013).

Depression is a heterogeneous disorder consisting of various symptoms and underlying aetiologies. To meet the DSM-5 criteria for a diagnosis of major depressive disorder (MDD) a person must have 5 out of 9 symptoms; at least one of these symptoms must be either depressed mood or loss of interest (American Psychiatric Association, 2013). This means that different persons can meet the criteria for major depression while having few symptoms in common. Symptom expression may be influenced by age. For instance, older adults are less likely to report depressed mood (Gallo, Anthony, & Muthen, 1994) and more likely to report motivational and somatic symptoms (i.e., loss of interest, concentration difficulties, sleep disturbance) compared to younger adults (Christensen, Jorm, et al., 1999; Fiske, Wetherell, & Gatz, 2009; Hegeman, Kok, van der Mast, & Giltay, 2012). Specific symptoms of depression may be differentially associated with cognitive dysfunctions. For instance, affective symptoms of depression may be more dominant in the early stages of cognitive impairment and may manifest as a psychological reaction to perceived cognitive problems in the early stages of impairment, whereas somatic and motivational symptoms of depression may be associated with a more chronic course of cognitive impairment and may be part of a prodromal syndrome of dementia (Bartolini, Coccia, Luzzi, Provinciali, & Ceravolo, 2005; Potvin, Hudon, Grenier, & Preville, 2010; K. Ritchie, Gilham, Ledésert, Touchon, & Kotzki, 1999).

Understanding the direction of influence between depression and cognitive dysfunctions, the timing of the effect, and the extent to which the effect varies as a function of the type of depression symptoms experienced, could have implications for the treatment of depression and for the prognosis of cognitive outcomes.

1.2 Chapter structure

In this chapter I consider background issues that have motivated the research investigations conducted for this thesis.

- I discuss the spectrum of cognitive decline from healthy ageing to various forms of dementia and the intermediate states such as mild cognitive impairment and mild neurocognitive disorders. I also discuss the quantitative and qualitative differences between healthy and pathological cognitive ageing.
- I discuss the role of brain reserve and cognitive reserve in maintaining optimal levels of cognitive functioning in late life.
- I briefly discuss evidence regarding cohort differences in cognitive functioning across the life-span, and then I review findings about cohort differences in levels and trajectories of cognitive performance in late life. I also mention the factors that may explain these cohort effects, with a special focus on educational attainment.
- I discuss differences between late-life depression and earlier-life depression in terms of prevalence and symptom presentation.
- I discuss the co-occurrence of cognitive dysfunctions with depression symptoms in late life, and the potential aetiological mechanisms underlying this association,

with a special focus on evidence that late-life depression may precipitate cognitive decline by reducing cognitive reserve.

- I review the evidence on the longitudinal direction of influence between depression symptoms and cognitive functioning in late life. I start by reviewing findings from studies that examined unidirectional prospective effects between depression and cognitive functioning. Evidence from these studies is discussed in light of several hypotheses regarding the association between depression and cognitive functioning, whereby depression may be a risk factor for cognitive decline, a prodromal syndrome of dementia, or a psychological reaction to perceived cognitive dysfunctions. I then review findings from studies that simultaneously examined longitudinal bidirectional associations between depression and cognitive functioning in late life with the aim to clarify the direction, timing and magnitude of the association between depression symptoms and various cognitive abilities.
- I discuss findings from studies that used a multi-dimensional approach to late-life depression to examine associations between specific depression symptom dimensions and various domains of cognitive functioning.
- I highlight the existing knowledge gaps and the research aims for this thesis, and I present the thesis structure.

1.3 Cognitive ageing

Although cognitive decline is a normal part of the ageing process there are significant individual differences in the rate of ageing-related cognitive decline

(Christensen, Mackinnon, et al., 1999; Wilson et al., 2002). Some individuals show minimal changes in cognitive functioning with age, whereas others show mild or moderate cognitive dysfunctions. A proportion of older adults will go on to develop dementia after crossing a relatively long preclinical phase (i.e., several years to several decades) characterised by progressive neuropathological changes and cognitive decline (Backman, Jones, Berger, Laukka, & Small, 2005; Schmid, Taylor, Foldi, Berres, & Monsch, 2013; Villemagne et al., 2013). Cognitive decline accelerates during the last few years that precede a diagnosis of dementia (Amieva et al., 2005).

In epidemiological studies of ageing cognitive functioning is generally assessed using cognitive ability tests designed to measure specific domains of cognition. Of note, tests of specific mental abilities do measure those abilities, but they all also reflect an underlying general intelligence factor “g”. The “g” factor explains the positive correlation between cognitive tests, also known as the “positive manifold” (Spearman, 1904). The general factor accounts for about 40% of the total variance in a comprehensive set of cognitive tests assessing a wide range of contents; about 20% to 50% of the total variance in an individual test is accounted for by specific factors/cognitive abilities, and a proportion of the total variance is due to random measurement error (Deary, Penke, & Johnson, 2010). General and specific factors of cognition can be extracted using methods such as bi-factor or second-order factor models, which require a large and diverse set of cognitive tests.

1.3.2 Normal and pathological cognitive ageing

1.3.2.1 Healthy cognitive ageing

Normal or healthy cognitive ageing is typically defined in terms of the absence of a diagnosis of dementia or in terms of normative levels of cognitive performance for a specific age group (Deary et al., 2009). Cognitive decline observed in normal ageing is relatively mild, static, and does not cause significant functional impairment. As part of the normal ageing process various cognitive abilities decline at different rates. From early adulthood there is progressive decline in fluid cognitive abilities (e.g., reasoning, processing speed, executive function, episodic memory), whereas crystallised cognitive abilities (e.g., vocabulary, recognition, numerical abilities, general knowledge, semantic and implicit memory) are relatively better preserved until older age and only show steeper decline in the late 70s (Christensen, 2001; Salthouse, 2009, 2012; Schaie & Willis, 2010). Crystallised abilities involve a rather automatic/implicit processing of information, whereas fluid abilities require more effortful processing and higher levels of cognitive resources. Variability in cognitive change scores increases with age especially for fluid cognitive abilities (Christensen, Mackinnon, et al., 1999).

1.3.2.2 Mild cognitive impairment

An intermediate state on the continuum from normal to pathological ageing is referred to as “mild cognitive impairment” (MCI) (Petersen et al., 1999). The original criteria for MCI was the presence of memory impairment (Petersen et al., 1999), but later studies acknowledged MCI as a heterogeneous condition and revised criteria were developed that included the presence of objective impairment in various

cognitive abilities, subjective awareness of cognitive changes, independence in activities of daily living, and the absence of a dementia diagnosis (Albert et al., 2011). Unlike individuals with dementia who suffer from progressive and often irreversible cognitive deterioration, individuals with MCI may go on to develop dementia or revert to normal levels of cognition (Koepsell & Monsell, 2012; Mitchell & Shiri-Feshki, 2009). Reversion from MCI to normal cognition is more common in younger old persons, whereas conversion from MCI to dementia is more common in older old persons (Gao et al., 2014). The intermediate state between healthy cognitive ageing and dementia offers a window of opportunity for interventions to reverse or slow down cognitive decline (Prince et al., 2014).

1.3.2.3 Mild neurocognitive disorders

The Diagnostic and Statistical Manual of Mental Disorders (5th edition) includes a category named neurocognitive disorders (NCD), which can be mild or major. The subcategory of mild NCD was derived based on research on MCI and defines an intermediate state between healthy cognitive ageing and dementia. To meet the criteria for mild neurocognitive disorders the person must show noticeable decrement in cognitive functioning from previous levels (assessed with standardised neuropsychological tests or validated clinical measures), and cognitive deficits should not interfere with the activities of daily living (American Psychiatric Association, 2013). The subcategory of major NCD replaces the DSM-IV category “dementia or other debilitating conditions”. The revised criteria emphasise that conclusions about the severity of neurocognitive disorders should rely on age- and education-based normative data. It is also emphasised that mild and severe neurocognitive disorders exist on a continuum of impairment and do not represent

distinct categories. Persons with mild NCD may progress to dementia, revert to normal cognition, or remain mildly impaired. The intermediate state between healthy ageing and dementia offers potential for intervention to slow down cognitive decline and reduce the rates of dementia or delay its onset.

1.3.2.4 Dementia

Cognitive dysfunctions observed in dementia are severe, progressive, and associated with significant functional impairment. The specific cognitive dysfunctions observed in the early/preclinical period may differ from one type of dementia to another, but cognitive deficits become more widespread as patients progress to severe dementia. Alzheimer's Disease (AD) is the most frequent type of dementia, accounting for about 50% to 70% of cases (Winblad et al., 2016). Amyloid plaques and neurofibrillary tangles are the core pathological hallmarks of AD (Winblad et al., 2016). Difficulties remembering recent events is one of the main early manifestations of AD (Ballard et al., 2011; Winblad et al., 2016). Vascular dementia is a heterogeneous condition caused by a variety of pathologies (e.g., white matter lesions, lacunar infarcts and basal ganglia infarcts) (Kalaria & Erkinjuntti, 2006), and it is commonly associated with dysfunctions in semantic memory, executive, attentional, visuospatial and perceptual skills (Graham, Emery, & Hodges, 2004). Frontotemporal dementia is a group of degenerative dementias characterised by selective atrophy of the frontal and temporal lobes and by impairment in executive function, language, and performance monitoring (Hutchinson & Mathias, 2007). Dementia with Lewy Bodies is caused by deposits of an abnormal protein called "alpha-synuclein" inside brain cells; deficits in frontal-executive, attentional and visuo-spatial functions are predominant in these patients, whereas memory

ability is generally better preserved than in AD (Salmon et al., 1996). Abnormalities in brain processing of alpha-synuclein are also found in persons with Parkinson's dementia. Persons with Parkinson's dementia show extrapyramidal motor symptoms as well as predominant deficits in attention, memory and frontal-executive functions. The differential diagnosis between Parkinson's dementia and dementia with Lewy Bodies is complicated by the similarity in aetiologies and symptom presentations. In Parkinson's dementia motor symptoms typically precede cognitive symptoms, whereas in dementia with Lewy Bodies cognitive symptoms precede or co-occur with motor symptoms (Aarsland, 2016). Mixed dementia pathologies are common and their interplay can precipitate the clinical manifestation of dementia. For instance, 66% of patients with Lewy Bodies Dementia and 77% of patients with vascular dementia had also AD pathology (Barker et al., 2002). Recent advancements include the use of MRI and PET studies to track disease pathology in the brains of living persons with dementia, and to estimate how disease progression varies as a function of factors such as brain reserve, genes, comorbidities, or drug treatments (Ewers et al., 2011; Thompson et al., 2007).

1.3.2.5 Normal versus pathological cognitive ageing - qualitative or quantitative differences

There is debate on whether the distinction between normal and pathological cognitive ageing is qualitative or rather quantitative in nature (Spaan & Walla, 2016). Theories of qualitative differences in cognitive ageing suggest that dementia is not an exaggeration of the ageing process, but rather a distinct condition from normal cognitive ageing, underlined by distinct neuropathological and behavioural changes. With regard to neuropathological changes, previous findings suggest that both

normally-ageing individuals and individuals with AD show frontal lobe changes, but only individuals with AD show a marked reduction in hippocampal volume, a brain region that regulates memory processes (Head, Snyder, Girton, Morris, & Buckner, 2005). Also a specific neural loss in the CA1 region of the hippocampus was found in persons with AD, but not in normally ageing individuals (West, Coleman, Flood, & Troncoso, 1994). Moreover, while certain cognitive changes may appear to be similar in people with dementia and those without dementia, the underlying mechanisms may be different. For instance, in healthy ageing individuals memory difficulties may be secondary to executive function decline, whereas in individuals with AD memory decline may be a primary process driven by a dysfunction of the medial temporal lobe (Buckner, 2004; Milwain & Iversen, 2002).

Theories of quantitative differences in cognitive ageing postulate that healthy ageing and dementia are extremes that lie on the same continuum, that the same causes and mechanisms underlie normal cognitive ageing and dementia, and that the same interventions could impact on both conditions (Berg, 1985). One line of evidence in support of this hypothesis comes from findings showing that the prevalence of dementia increases dramatically with age. Given that dementia is diagnosed in a fifth of persons aged 85+, a third of those aged 90+, and half of those aged 95+ (Heeren, Lagaay, Hijmans, & Rooymans, 1991), it can be speculated that dementia itself may be part of normal cognitive ageing and that most older adults would develop dementia if they lived long enough (Berg, 1985). Another argument comes from studies showing that AD neuropathology (i.e., plaques and tangles) occurs not only in AD but also in older adults with normal cognitive functioning (Price & Morris, 1999). Persons diagnosed with dementia often show similar

neuropathology as those who died dementia free, albeit in different proportions (e.g., neocortical neurofibrillary pathology was found in 61% of persons with dementia and 34% of dementia-free individuals, whereas vascular lesions were found in 46% of persons with dementia and 33% of persons without dementia) (Esiri et al., 2001). These findings suggest that the absence of a dementia diagnosis is not necessarily an indicator of normal brain ageing. A final argument is based on the finding that dementia and accelerated cognitive decline in the general population share a common set of risk factors, such as low physical activity, low educational attainment/low cognitive reserve, depression, cardiovascular disease, diabetes, obesity, and smoking (Beydoun et al., 2014; Blondell, Hammersley-Mather, & Veerman, 2014; Caamano-Isorna et al., 2006; Deckers et al., 2015; Fillit, Nash, Rundek, & Zuckerman, 2008; Lee et al., 2010; Meng & D'Arcy, 2012; Plassman, Williams, Burke, Holsinger, & Benjamin, 2010; Valenzuela & Sachdev, 2006; Williams, Plassman, Burke, & Benjamin, 2010). This suggests that interventions targeting the same modifiable risk factors could help improve cognitive outcomes across the full spectrum of cognitive ageing, from healthy to pathological ageing.

Instead of dividing normal ageing and dementia into dichotomous outcomes, it may be of interest to examine cognitive ageing as a continuous multidimensional phenomenon. The use of repeated measures of cognitive abilities could help clarify protective and risk factors associated with different trajectories of cognitive ageing, which may be an important step for the early detection of individuals at risk for cognitive impairment and dementia.

1.3.2.6 Living with cognitive impairment and dementia

Older adults with MCI are able to engage in self-care behaviours, but they may have more difficulty performing certain activities of daily living (e.g., social conversations, driving, medication management) than healthy older adults (for a review see Lin, Vance, Gleason, & Heidrich, 2012). Persons with MCI are often able to identify their cognitive symptoms and describe their reaction to MCI (e.g., loss of self-confidence); their psychological well-being (e.g., life satisfaction, mastery, social interaction) is similar to that of healthy elders, and they are able to engage in self-help behaviors and use supportive services aimed at slowing down cognitive decline (Lin et al., 2012).

As dementia progresses the ability of older adults to work, maintain meaningful relationships, and perform activities of daily living is gradually impaired, and patients often experience a loss of awareness about their cognitive dysfunctions and a loss of control over their lives (Steeman, de Casterle, Godderis, & Grypdonck, 2006). The diagnosis of dementia has a strong impact on identity, causing feelings of loss, anger, uncertainty, and frustration, as well as social isolation (Bunn et al., 2012). Most behavioural and psychological symptoms of dementia (e.g., aggressiveness, wandering, restless behavior, depressive symptoms) are predominant in the moderate stages of dementia, but apathy is more frequent in more severe stages of dementia (Lovheim, Sandman, Karlsson, & Gustafson, 2008). Persons with dementia need greater levels of social and psychological support after diagnosis, and they often perceive peer support as valuable (Bunn et al., 2012). Positive relationships with carers play an important role in maintaining quality of life in early-stage dementia (Clare et al., 2014). Persons who assume the role of carers for their

partners with dementia need to adjust to unequal relationships, and they may experience psychological strain (e.g., symptoms of depression, anxiety, loneliness) and coping difficulties especially in the early stages of dementia when more adjustment is needed (Bunn et al., 2012).

1.3.3 Maintaining cognitive functioning in old age - brain reserve and cognitive reserve

The concept of “reserve” was proposed to account for the observation that persons with a given level of brain pathology differ in the clinical manifestation of that pathology (Stern, 2002). Brain reserve and cognitive reserve are related constructs. Brain reserve may refer to synaptic density and the ability to recruit flexibly and efficiently brain networks that are less affected by pathology (Katzman et al., 1988), whereas cognitive reserve may refer to the efficient use of cognitive strategies that could help optimize cognitive performance (Stern, 2003). Persons who use brain networks and cognitive strategies more efficiently may sustain higher levels of neuropathological burden (i.e., white matter hyperintensities) before cognitive impairment manifests (i.e., executive function, processing speed and language ability) (Brickman et al., 2011).

Educational attainment is the most frequently used proxy measure for cognitive reserve; other proxy measures include occupational attainment and involvement in cognitively stimulating activities (Opdebeeck et al., 2016). Evidence from meta-analyses and systematic literature reviews suggests that higher educational attainment is related to lower risk of dementia (Beydoun et al., 2014; Caamano-Isorna et al., 2006; Meng & D'Arcy, 2012), lower risk of mild cognitive

impairment (Luck et al., 2010), slower rates of cognitive decline (Valenzuela & Sachdev, 2006), and improved cognitive performance in healthy older adults (Opdebeeck et al., 2016). Recent evidence suggests that education explains individual differences in specific cognitive abilities “s”, but not in the general factor “g”. Consistent with Spearman’s observation (Spearman, 1927), these findings suggest that longer schooling may help optimize specific cognitive abilities, rather than general intelligence (S. J. Ritchie, Bates, & Deary, 2015).

Educational attainment may influence cognitive functioning in old age through several mechanisms. First, education may impact on cognitive performance by reducing age-related cortical atrophy and the occurrence of cerebral infarcts, or by optimising cognitive strategies to compensate for neuropathological burden (Coffey, Saxton, Ratcliff, Bryan, & Lucke, 1999; Del Ser, Hachinski, Merskey, & Munoz, 1999; Pinto & Tandel, 2016). Second, higher educational attainment may be related to higher socio-economic status which offers an advantage in terms of lifestyle and health behaviours (e.g., smoking, diet, physical activity, depression) (Cavelaars et al., 2000; Fong et al., 2007; Nédó & Paulik, 2012; Peyrot et al., 2015), leading to better cognitive outcomes in late life (Beydoun et al., 2014; Blondell et al., 2014; Deckers et al., 2015; Lee et al., 2010). Third, persons with more years of schooling get more practice with cognitive test taking which may lead to better performance on cognitive tests. It should be noted that the relation between education, brain reserve, and cognitive functioning in late-life is complex and likely multidirectional. Longer duration of education may improve cognitive outcomes in late-life, but education duration itself may depend on prior cognitive ability levels. Genetic links have been

found with educational attainment (Rietveld et al., 2013) and with the stability of cognitive ability across the lifespan (Deary et al., 2012).

Whereas education helps build cognitive reserve earlier in life, occupational attainment and participation in cognitively stimulating activities may contribute to maintaining and further developing cognitive reserve later in life (Wight, Aneshensel, & Seeman, 2002). These factors have been shown to have both individual and combined effects on cognitive performance in healthy older adults (Opdebeeck et al., 2016).

1.3.4 Cohort differences in cognitive functioning across the life-span

During the past century later born cohorts have consistently outperformed earlier born cohorts of similar age on intelligence tests. (Flynn, 1987; Schaie, Willis, & Pennak, 2005). Findings by Flynn (1987) suggest an increase in IQ scores of up to 1.5 standard deviation in 19-year-old persons born after World War II (tested in 1980) compared to 19-year-olds born during the Great Depression (tested in 1950). This finding, known as the “Flynn effect”, was reported across 14 developed countries, and the effect was stronger for fluid abilities than for crystallised abilities. (Flynn, 1987, 2007). Other studies confirmed that cohort differences in cognitive performance manifest across the lifespan, from early childhood until late life (e.g., Bowles, Grimm, & McArdle, 2005; Pietschnig & Voracek, 2015; Rodgers, 1998; Ronnlund & Nilsson, 2009; Skirbekk et al., 2013; Trahan, Stuebing, Fletcher, & Hiscock, 2014; Wongupparaj, Kumari, & Morris, 2015), and across both developed and developing countries (Wongupparaj et al., 2015).

1.3.5 Cohort differences in cognitive performance and rates of decline in late life

Most of the studies that examined cohort differences in levels of cognitive performance in late life reported that later born cohorts showed better performance in various cognitive domains compared to earlier born cohorts (i.e., positive cohort effects; see Table 1) (Baxendale, 2010; Christensen et al., 2013; Dodge et al., 2014; Finkel et al., 2007; Gerstorf et al., 2011; Karlsson, Thorvaldsson, Skoog, Gudmundsson, & Johansson, 2015; Zelinski & Kennison, 2007). No study reported better levels of cognitive performance in earlier born cohorts compared to later born cohorts (i.e., negative cohort effects; see Table 1). Only a few studies reported no cohort differences in certain cognitive abilities (i.e., processing speed, list learning and numeric ability) (Baxendale, 2010; Finkel et al., 2007).

Although there is general agreement that later born cohorts show better levels of cognitive performance than earlier born cohorts, evidence on cohort differences in the rates of cognitive decline is mixed. (see Table 2). Some findings provided support for the *preserved differentiation* hypothesis (Salthouse, 2006) whereby cohort differences in cognitive performance are similarly preserved over time, resulting in parallel trajectories of cognitive decline between cohorts (Dodge et al., 2014; Finkel et al., 2007; Zelinski & Kennison, 2007). Other findings provided support for the *differential preservation* hypothesis (Salthouse, 2006), whereby later born cohorts show either shallower cognitive decline (Dodge et al., 2014; Gerstorf et al., 2011; Zelinski & Kennison, 2007), or steeper cognitive decline than earlier born cohorts of the same age (Karlsson et al., 2015; Zelinski & Kennison, 2007).

There is evidence that cohort differences in levels and trajectories of cognitive performance may level out in the final years of life due to the pervasive nature of terminal decline (see Table 3) (Gerstorf et al., 2011; Hult, Infurna, Ram, & Gerstorf, 2013).

In the global context of population ageing and related health care concerns, the finding that cohort improvements in cognitive performance may persist into late life holds promise for extending the window of healthy and productive ageing. On one hand, given that age is the best predictor of cognitive decline, and that recently born cohorts have a higher life expectancy than earlier born cohorts, the average level of cognitive performance at the population level may be lower in more recently born cohorts. On the other hand, given that recently-born more educated cohorts are replacing earlier-born less educated cohorts, the average level of cognitive performance at the population level may be similar between cohorts or higher in more recently born cohorts. (Skirbekk et al., 2013). It is projected that a continuation of cohort improvements in cognitive functioning (2008-2042) that are at least a third of those observed in the past (i.e., birth cohort 1930-1949 and birth cohort 1936-1955, both assessed between 2002-2008) could offset the negative effects of population ageing (Skirbekk et al., 2013).

Table 1. Cohort differences in cognitive performance in late life

Study	Positive cohort effects	Negative cohort effects	No cohort effect	Age	Birth cohort
Finkel et al. (2007)	memory, verbal and spatial ability;	×	processing speed;	67.5	1900-1925 1926-1948
Zelinski & Kennison (2007)	reasoning, spatial orientation, list recall, test recall and vocabulary;	×		74	1893-1923 1908-1940
Baxendale (2010)	list recall, visual learning and visual recall;	×	list learning;	61 - 75	1910-1924 1932-1946
Gerstorf et al. (2011)	spatial orientation, word fluency, inductive reasoning, and verbal meaning;	×	numeric ability;	70	1886-1913 1914-1948
Christensen et al. (2013)	general cognitive performance and a composite score of five cognitive abilities;	×	×	93 95	1905 1915
Dodge et al. (2014)	psychomotor speed, executive function, letter fluency and category fluency;	×	×	65	1902-1911 1912-1921 1922-1931 1932-1943
Karlsson et al. (2015)	logical reasoning and spatial ability;	×	×	70	1901-1902 1906-1907 1930
Gerstorf et al. (2015)	perceptual speed;	×	×	75	1901-1922 1925-1948

Note: Positive cohort effects are defined as better cognitive performance in later born cohorts; negative cohort effects are defined as better cognitive performance in earlier born cohorts.

Table 2. Cohort differences in rates of cognitive decline in late life

Study	Cognitive domain	Age	Follow-up	Birth cohort
<i>No cohort effects</i>				
Finkel et al. (2007)	verbal, spatial, memory, and processing speed abilities;	62 - 78	16 years	1900 - 1925 1926 - 1948
Dodge et al. (2014)	psychomotor speed, category fluency;	65 and above	6 years	1912 - 1921 1922 - 1931 1932 - 1943
	letter fluency;			1922 - 1931 1932 - 1943
Zelinski & Kennison (2007)	reasoning, text and list recall, vocabulary, spatial ability;	56 - 71	9-22 years	1893 - 1923 1908 - 1940
	reasoning, spatial ability;	77 - 86	9-22 years	1893 - 1923 1908 - 1940
<i>Positive cohort effects</i>				
Gerstorf et al. (2011)	spatial orientation, inductive reasoning, word fluency, numeric ability, verbal meaning;	50 - 80	49 years	1886 - 1913 1914 - 1948
Zelinski & Kennison (2007)	Vocabulary;	77 - 86	9-22 years	1893 - 1923 1908 - 1940
Dodge et al. (2014)	executive function;	65 and above	6 years	1902 - 1911 1912 - 1921 1922 - 1931 1932 - 1943
	letter fluency;	65 and above	6 years	1902 - 1911 1912 - 1921 1932 - 1943
	psychomotor speed, category fluency;	65 and above	6 years	1902 - 1911 1932 - 1943
<i>Negative cohort effects</i>				
Zelinski & Kennison (2007)	text and list recall;	77 - 86	9-22 years	1893 - 1923 1908 - 1940
Karlsson et al. (2015)	spatial ability, reasoning ability.	70 - 79	9 years	1901 - 1902 1906 - 1907 1930

Note: Positive cohort effects are defined as better cognitive performance in later born cohorts; negative cohort effects are defined as better cognitive performance in earlier born cohorts.

Table 3. Cohort differences in terminal cognitive performance and cognitive decline

Study	Positive cohort effects	Negative cohort effects	No cohort effect	Age	Cohort
<i>Terminal cognitive performance</i>					
Gerstorff et al. (2011)	verbal meaning;	numeric ability;	inductive reasoning, spatial ability, word fluency;	3 years before death	Birth cohort 1886-1913 1914-1948
Hulur et al. (2013)	×	episodic memory;	×	80	Death cohort 1993–1999 2000 –2010
<i>Terminal cognitive decline</i>					
Gerstorff et al. (2011)	verbal meaning;	inductive reasoning, spatial ability, numeric ability, word fluency;	×	50-80	Birth cohort 1886-1913 1914-1948
Hulur et al. (2013)	×	episodic memory;	×	70 and above	Death cohort 1993–1999 2000 –2010

Note: Positive cohort effects are defined as better cognitive performance in later born cohorts; negative cohort effects are defined as better cognitive performance in earlier born cohorts.

1.3.6 Factors contributing to cohort differences in cognitive ageing – the role of cognitive reserve

Cohort differences in levels and trajectories of cognitive performance may reflect the cumulative impact of a variety of factors such as improvements in education and occupational attainment, nutrition, technology, health care, and health behaviours (Neisser, 1997). The extent to which the above factors may account for cohort differences in cognitive ageing is unclear.

Although the Flynn effect has been documented worldwide over the past century, there is still debate on whether cohort improvements in cognitive performance reflect genuine gains in cognitive abilities or rather greater familiarity with cognitive test taking amongst more highly educated persons. Moreover, standardized cognitive tests do not measure every possible form of intelligence. It is possible that current cognitive tests measure certain forms of intelligence that may be more characteristic of later born cohorts (i.e., abstract reasoning, memory, problem solving), rather than intelligence that may be more characteristic of earlier born cohorts (i.e., practical sense, creativity). Although more years of schooling in later born cohorts should result in better performance on abilities which are trained in school, such as vocabulary or arithmetic (i.e., crystallized abilities), the highest gains have been observed on abstract reasoning tests (e.g., Raven's Progressive Matrices). This suggests that the Flynn effect may not be fully explained by greater familiarity with cognitive tests and improved test taking strategies in later born cohorts.

Given the increase in educational attainment over the past century (Breen, Luijkx, Muller, & Pollak, 2010), and in view of evidence that schooling helps

increase cognitive reserve (Stern, 2006), education may be a primary candidate able to account for cohort differences in cognitive functioning in late life. Previous studies suggest that higher educational attainment predicts higher levels of cognitive performance in older age (e.g., Glymour, Kawachi, Jencks, & Berkman, 2008; Schneeweis, Skirbekk, & Winter-Ebmer, 2014; van Hooren et al., 2007), but there is little consistent evidence that higher education may slow down ageing-related cognitive decline (for a review see Lenehan, Summers, Saunders, Summers, & Vickers, 2015). The extent to which educational attainment may account for cohort differences in levels and trajectories of cognitive performance is unclear. Karlsson et al. (2015) found that education accounted for cohort differences in levels of performance and rates of decline in spatial ability, but not reasoning ability. Other studies found that cohort differences in levels and trajectories of cognitive performance (i.e., processing speed, executive function, language ability, spatial orientation, inductive reasoning, word fluency, verbal meaning, general cognitive performance) persisted after adjusting for educational attainment (Christensen et al., 2013; Dodge et al., 2014; Gerstorf et al., 2015; Gerstorf et al., 2011).

The effect of educational attainment on cohort differences in levels and trajectories of cognitive performance needs further investigation. The *preserved differentiation* hypothesis suggests a passive role of cognitive reserve whereby initial differences in cognitive performance between cohorts with more or fewer years of education are similarly preserved over time resulting in similar/parallel rates of cognitive decline (Salthouse, 2006). The *differential preservation* hypothesis on the other hand suggest either an active role or a compensatory role of cognitive reserve (Salthouse, 2006). If cognitive reserve plays an active role against ageing-related

cognitive decline, then later born cohorts (i.e., more educated) would show slower rates of cognitive decline than earlier born cohorts (i.e., less educated) because they are better able to compensate for neuropathological changes. If cognitive reserve plays a compensatory role against ageing-related cognitive decline, then later born cohorts (i.e., more educated) would maintain better cognitive performance into older age but they may show steeper cognitive decline than earlier born cohorts (i.e., less educated) once a certain threshold of neuropathological burden is reached and compensatory mechanisms are exhausted.

1.4 Late-life depression

Depression in late life is associated with high economic, public health and caregiver burden (Zivin, Wharton, & Rostant, 2013). Depression is a multi-dimensional condition consisting of various symptoms such as depressed mood, reduced positive affect, and somatic complaints. To meet the DSM-5 criteria for a diagnosis of major depressive disorder a person must have 5 out of 9 symptoms: depressed mood, diminished interest or pleasure, significant changes in weight or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or loss of energy, feelings of guilt or worthlessness, concentration difficulties, recurrent thoughts of death. These symptoms must be present during a period of at least 2 weeks and should cause significant distress or functional impairment; at least one of the symptoms must be either (1) depressed mood, or (2) loss of interest or pleasure (American Psychiatric Association, 2013). This leads to a wide heterogeneity of symptom presentations whereby two persons can meet the criteria for MDD while having only one symptom in common. The prevalence and symptom presentation of

late-life depression is different from depression earlier in life (Blazer, 2003). Compared to younger adults, older adults have a lower prevalence of MDD (Kessler et al., 2010), but a higher prevalence of subsyndromal depression (Meeks, Vahia, Lavretsky, Kulkarni, & Jeste, 2011). These findings suggest that the use of DSM criteria for a diagnosis of depression in late life may be too restrictive and could lead to a large number of undiagnosed and untreated persons who experience subsyndromal depressive symptoms of clinical significance, with substantial impact on public health. Therefore, depression rating scales that are validated among older adults may be more suitable for identifying clinically relevant symptoms of late-life depression.

Moreover, there is evidence that older adults express lower levels of depressed affect (e.g., sadness, crying, guilt) (Gallo et al., 1994), but more pronounced somatic symptoms (e.g., fatigue, sleep disturbance, loss of appetite) and motivational symptoms of depression (e.g., lack of interest or enjoyment, concentration difficulties) compared to younger adults (Christensen, Jorm, et al., 1999; Fiske et al., 2009; Hegeman, Kok, et al., 2012). A dimensional approach to late life depression may help clarify the aetiologies underlying different symptom presentations (Hegeman, Wardenaar, et al., 2012).

1.5 Depression and cognition in late life

Late-life depression often co-occurs with impairment in cognitive abilities such as executive function, processing speed, and episodic memory (Baudic, Tzortzis, Barba, & Traykov, 2004; Lockwood, Alexopoulos, & van Gorp, 2002; Sheline et al., 2006). Cognitive dysfunctions are associated with poor response to

antidepressant treatment (Alexopoulos et al., 2005; Alexopoulos et al., 2000; Kalayam & Alexopoulos, 1999; Potter, Kittinger, Wagner, Steffens, & Krishnan, 2004; Story, Potter, Attix, Welsh-Bohmer, & Steffens, 2008), and they may persist after remission from a depressive episode (Kohler, Thomas, Barnett, & O'Brien, 2010; Nebes et al., 2003).

A proportion of older adults with depression in late life have experienced their first depression episode in the first decades of life (i.e., early-onset depression), whereas others experience their first depression episode in late life (i.e., late-onset depression). Late-onset depression may differ from early-onset depression in terms of aetiology, clinical presentation and associations with cognitive deficits. Persons with early-onset depression are more likely to have a family history of depression (Heun, Papassotiropoulos, Jessen, Maier, & Breitner, 2001) and to show comorbid personality disorders and neuroticism (Brodaty et al., 2001). Persons with late-onset depression are more likely to have vascular risk factors (Hickie et al., 2001), deep white matter lesions (Schweitzer, Tuckwell, O'Brien, & Ames, 2002), and cognitive impairment in abilities that rely on frontal efficacy (i.e., executive function, attention, processing speed) (Herrmann, Goodwin, & Ebmeier, 2007).

1.5.1 Aetiological mechanisms underlying the association between depression and cognitive dysfunctions in late life

The co-occurrence of depression symptoms and cognitive deficits may reflect an underlying process linked to the clinical onset of dementia. Elevated levels of glucocorticoids observed in depression may promote hippocampal cell injury and precipitate AD pathogenesis and related memory-dysfunctions (Butters et al., 2008).

Higher levels of hippocampal amyloid plaque and neurofibrillary tangle pathology have been observed in patients with Alzheimer Disease who also show comorbid depression or a history of depression, compared to persons without depression (Rapp et al., 2006). Also, vascular lesions in the brain may disrupt frontostriatal pathways (Schneider, Ercoli, Siddarth, & Lavretsky, 2012), leading to executive function and processing speed deficits, as well as an increase in motivational symptoms of depression (e.g., loss of energy and interest, concentration difficulties, psychomotor retardation) rather than an increase in affective symptoms (e.g., feelings of guilt and sadness, suicidal thoughts) (Alexopoulos, 2001, 2006; Li, Meyer, & Thornby, 2001).

Brain and cognitive reserve may be possible pathways linking depression to cognitive dysfunctions and dementia. Depression may modify the threshold of manifestation of cognitive dysfunctions and dementia by lowering cognitive reserve (Butters et al., 2008). Depression may lower brain reserve by increasing the risk for cerebrovascular disease and by increasing hippocampal injury burden through elevated glucocorticoid production, amyloid deposition, and neurofibrillary formation (Butters et al., 2008). Depression may also exacerbate decline in cognitive reserve indirectly by reducing participation in social, physical and leisure cognitive activities (Fiske et al., 2009), all of which have been linked to accelerated cognitive decline and an increased risk of dementia (Beydoun et al., 2014; Blondell et al., 2014; Hamer & Chida, 2009; Kuiper et al., 2015; Sofi et al., 2011).

Depression symptoms and low educational attainment may have synergistic effects on impeding cognitive performance in old age. This hypothesis is supported by evidence from a systematic review suggesting a stronger negative association

between depression symptoms and cognitive performance in persons with lower cognitive reserve (i.e., operationalised as educational attainment in most studies) (Opdebeeck, Quinn, Nelis, & Clare, 2015). However, some studies failed to find this effect. Bhalla et al. (2005) found no interaction effect between depression diagnosis and educational attainment on cognitive performance, whereas O'Shea et al. (2015) found a stronger negative association between depression and cognitive performance (i.e., memory, language, executive function) in persons with higher educational attainment. A study conducted in older adults without cognitive impairment found that depression predicted an increased risk of cognitive decline and AD only among persons with higher levels of education (Geerlings et al., 2000). A potential interpretation of the findings by O'Shea et al. (2015) and Geerlings et al. (2000) is that persons with lower cognitive reserve have already shown poorer levels of cognitive functioning, so they may have less room for cognitive decline in the presence of depression symptoms than persons with higher cognitive reserve. Also, depression could manifest as an early syndrome of dementia in more highly educated persons. Higher cognitive reserve (built through education) could help delay cognitive symptoms of AD, but not the depression symptoms (Geerlings et al., 2000). The discrepant findings regarding the moderating effect of educational attainment on the relation between depression and cognitive functioning may be partly explained by differences between studies in the levels of educational attainment and in the measures employed to assess depression and cognition in older adults.

1.5.2 Longitudinal associations between depression symptoms and cognitive dysfunctions in late life

Although extensive evidence suggests that cognitive dysfunctions and depressive symptoms co-occur in late life, there is no clarity regarding the direction of influence between cognitive dysfunction and depression symptoms. Depression may act both as an independent risk factor for dementia (i.e., depression episodes earlier in life) and as a prodromal syndrome of dementia (i.e., depression accompanying cognitive decline in late-life). Cumulative depression burden over the life course (in terms of symptom severity, duration and number of MDD episodes) increases the risk for dementia (Butters et al., 2008). Moreover, depression symptoms may reflect a psychological reaction to perceived cognitive decrements in the early stages of impairment. More research is needed to understand the direction and timing of the association between depression symptoms and late-life cognitive functioning.

Does depression precede cognitive impairment and dementia?

Growing evidence from systematic reviews and meta-analytic studies suggests that baseline depressive symptoms or major depression predict an elevated risk of cognitive decline (Williams et al., 2010), and incident dementia (Cherbuin, Kim, & Anstey, 2015; Diniz, Butters, Albert, Dew, & Reynolds, 2013; Ownby et al., 2006; Prince et al., 2014). Cumulative depression burden over the lifespan, in terms of symptom severity and the number of depression episodes, may increase the risk for cognitive impairment and dementia (da Silva, Goncalves-Pereira, Xavier, & Mukaetova-Ladinska, 2013; Dotson, Beydoun, & Zonderman, 2010; Kessing &

Andersen, 2004). Although these findings suggest that depression precedes cognitive deterioration, it is not clear whether depression is a true risk factor for cognitive decline and dementia, or whether depression is a prodromal syndrome of dementia. In one scenario, if depression were a true causal risk factor for cognitive impairment/dementia, then episodes of depression would precede cognitive dysfunctions over a relatively long time interval. In another scenario, if depression is a prodromal syndrome of dementia, then depression may precede cognitive dysfunctions/dementia over a relatively short interval.

Support for the hypothesis that depression may be an independent risk factor for cognitive decline rather than a prodromal syndrome of dementia comes from a study showing that higher levels of depressive symptoms at baseline predicted steeper cognitive decline even after adjusting for neuropathological hallmarks of dementia (Wilson et al., 2014). Further support for this hypothesis is provided by a meta-analysis and meta-regression conducted by Ownby et al. (2006) which found that persons with a history of clinically diagnosed depression had a higher risk of incident AD compared to persons without a history of depression, and that the magnitude of this effect was higher in studies with a longer follow-up period.

Support for the hypothesis that depression may be a prodromal syndrome of dementia rather than an independent risk factor comes from a meta-analysis and meta-regression conducted by Prince et al. (2014) which found a trend for a stronger association between depression and incident all-cause dementia in studies with shorter follow-up durations.

Finally, support for the hypothesis that depression may modify the threshold of manifestation of dementia comes from meta-analytic evidence suggesting a higher rate of conversion from MCI to dementia in persons with depression symptoms compared to persons without depression symptoms (Mourao, Mansur, Malloy-Diniz, Castro Costa, & Diniz, 2015). This suggests that MCI, depression, and dementia may be stage-specific manifestations of a common clinical phenomenon.

Does cognitive impairment and dementia precede depression?

Evidence regarding the effect of cognitive impairment on depression is mixed. A systematic review of longitudinal studies concluded that 3 out of 5 studies did not find a significant effect of cognitive impairment on incident depression (Cole & Dendukuri, 2003). Another meta-analysis of 13 cross-sectional and 4 longitudinal studies found an increased prevalence and incidence of depression in persons with a diagnosis of dementia, but not in those with cognitive impairment (Huang, Wang, Li, Xie, & Liu, 2011). Due to the scarcity of longitudinal studies that investigated the prospective effect of cognitive impairment or dementia on incident depression it is not possible to draw firm conclusions regarding this direction of the effect.

Are there bidirectional longitudinal associations between depression symptoms and cognitive functions?

Most of the longitudinal studies that investigated the relation between depression and cognitive functioning in late life examined only one direction of the effect (i.e., depression preceding cognitive decline, or poor cognitive functioning preceding an increase in depression symptoms). To overcome problems of reverse causation, a number of longitudinal studies have simultaneously investigated

bidirectional associations between depression symptoms and cognitive functioning, in order to determine the relative magnitude of the prospective associations (i.e., whether initial depression levels predict subsequent cognitive performance better than initial cognitive performance predicts subsequent depression levels; see Table 4). Four out of seven studies (with follow-up durations between 3.5 years and 13 years) found that persons with higher initial depression scores showed steeper cognitive decline over time (Bunce, Batterham, Christensen, & Mackinnon, 2014; Gale, Allerhand, Deary, & Team, 2012; Panza et al., 2009; Vinkers, Gussekloo, Stek, Westendorp, & van der Mast, 2004), whereas initial levels of cognitive performance did not predict levels of depression at a later time point. Two studies (with follow-up durations between 2 years and 3 years) found evidence for the opposite direction of the effect whereby persons with poorer initial cognitive scores showed a higher increase in depression symptoms over time (Jajodia & Borders, 2011; Perrino, Mason, Brown, Spokane, & Szapocznik, 2008), whereas initial depression levels did not predict levels of cognitive performance at a later time point. One study (with a follow-up duration of 13 years) found evidence for both directions of the effect, but only for the association between depression symptoms and processing speed (van den Kommer et al., 2013). Additionally, the study by van den Kommer et al. (2013) examined associations between changes in depression symptoms and changes in cognitive functioning over time and found no significant effects. Based on the above-mentioned evidence it is not possible to draw firm conclusions about the direction and timing of the association between depression symptoms and cognitive functioning in late life. Methodologically robust studies allowing the simultaneous examination of bi-directional prospective associations, as well as synchronous

longitudinal associations, between depression symptoms and cognition functioning are needed to advance existing knowledge on this research topic.

Table 4. Longitudinal bidirectional associations between depression symptoms and cognitive functioning

Study	Age	Follow up duration	Higher initial depression → steeper cognitive decline	Poorer initial cognition → increase in depression
Gale <i>et al.</i> (2012)	60-80	8 years	- general cognitive function	n.s.
	50-60	8 years	n.s.	n.s.
Panza <i>et al.</i> (2009)	65-84	3.5 years	- global cognitive function - delayed recall, - <i>not</i> immediate recall	n.s.
van den Kommer <i>et al.</i> (2013)	55-85	13 years	- processing speed - general cognitive function	- processing speed - <i>not</i> general cognitive function
Bunce <i>et al.</i> (2014)	70-97	4 years	- processing speed - reaction time	n.s.
Vinkers <i>et al.</i> (2004)	85	5 years	- attention - immediate recall - delayed recall	n.s.
Perrino <i>et al.</i> (2008)	≥ 75	3 years	n.s.	- global cognitive function
Jajodia and Borders (2011)	≥ 50	2 years	n.s.	- delayed recall

Note: n.s. = effect is not statistically significant

1.5.3 Differential associations between specific dimensions of late-life depression and cognitive functioning

Most studies that investigated the relation between late-life depression and cognitive functioning in old age measured depression as a unidimensional construct and did not distinguish between different symptom dimensions. However, specific symptom presentations may reflect distinct aetiologies, and may be differentially related to the nature and course of cognitive impairment. There is evidence suggesting that affective symptoms of depression may manifest as a psychological reaction to perceived cognitive dysfunction in the early stages of impairment, whereas somatic symptoms (e.g., appetitive and sleep disturbance) and motivational symptoms (e.g., loss of interest in activities, concentration difficulties, psychomotor slowing) may be related to a more chronic course of cognitive impairment (Bartolini et al., 2005; K. Ritchie et al., 1999).

Previous findings suggest that symptoms such as fatigue, sleep disturbance, and cognitive complaints were associated with “cognitive impairment no dementia” in the absence of dysphoric and anhedonic symptoms (Potvin et al., 2010). Other studies suggest that motivational symptoms of depression (e.g., lack of interest, loss of energy, concentration difficulties) were dominant in the preclinical phase of Alzheimer Disease (Bartolini et al., 2005; Berger, Fratiglioni, Forsell, Winblad, & Backman, 1999), and in mild cognitive impairment (Kumar, Jorm, Parslow, & Sachdev, 2006). Symptoms of “motivational disturbance” showed stronger cross-sectional associations with verbal fluency impairment than “affective suffering” symptoms (Castro-Costa et al., 2007). Longitudinal findings from a study conducted

in patients with a history of vascular disease suggest that poor initial executive function, processing speed and memory performance was associated with a steeper increase in motivational and somatic symptoms of depression compared to mood symptoms over seven years of follow-up (Kooistra et al., 2015). These findings are consistent with the depression-executive dysfunction hypothesis according to which motivational symptoms of depression tend to occur in the context of executive deficits, possibly due to vascular disease and a disruption of frontal-subcortical pathways (Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002; Alexopoulos et al., 1997). However, other findings suggest that depressed affect and somatic symptoms were similarly related to cognitive performance on attention and motor tasks in the general population (Baune, Suslow, Arolt, & Berger, 2007).

Some lines of evidence suggest a link between positive affect and cognitive functioning in late life. Positive affect could help maintain cognitive function by reducing stress hormone levels and cardio-vascular risk, by improving health behaviours such as diet, sleep, and physical exercise, and by increasing the engagement in social interactions and cognitively stimulating activities (for a review see Pressman & Cohen, 2005). Cross-sectional findings suggest that higher positive affect was more strongly associated with cognitive performance (i.e., memory, psychomotor speed, mental status) than depressed affect, somatic symptoms or interpersonal difficulties (La Rue, Swan, & Carmelli, 1995). Also higher positive affect was related to better every day problem solving (Paterson, Yeung, & Thornton, 2016), and better verbal fluency performance, but not better memory, speed or attention (Baune et al., 2007). Longitudinal findings suggest that lower levels of positive affect (but not depressed affect, somatic symptoms or interpersonal

difficulties) were associated with steeper decline in global cognition, episodic memory, and perceptual speed (Turner, Capuano, Wilson, & Barnes, 2015).

More research is needed to clarify which symptoms of depression are more strongly associated with cognitive dysfunctions in late life, and what is the direction and timing of the effect.

1.6 Knowledge gaps and research aims

This thesis focuses on education and depression because both factors have widely reported links with cognitive function in old age. Furthermore, given that both are potentially modifiable intervention targets, my thesis provides a basis for informing on their potential clinical and policy relevance for improving cognitive health in late life. Persons with more years of schooling and lower depression symptoms may enter old age with better cognitive reserve and an edge in cognitive performance. More research is needed to understand the role of education and depression symptoms on levels and trajectories of cognitive performance in late life. Understanding the role of education as an underlying factor of late-life cognitive inequalities between birth cohorts has implications for extending the window of healthy cognitive ageing. Moreover, understanding which symptoms of depression are more strongly associated with poor cognitive functions, and what is the direction and timing of this relation, has implications for the treatment of depression and for the prognosis of cognitive outcomes.

Cohort differences in levels of cognitive performance and rates of cognitive decline

Existing evidence suggests that later born cohorts outperform earlier born cohorts of the same age on cognitive tasks and that these cohort effects are maintained in late life. However, the extent to which cohorts differ in their levels and trajectories of cognitive performance in various cognitive abilities is unclear. Moreover, the factors accounting for these cohort effects remain poorly understood, but one potential candidate is educational attainment. Higher educational attainment in later born cohorts may increase cognitive reserve leading to a superior preservation of cognitive performance and slower rates of cognitive decline in late life.

Based on previous findings, I hypothesise that the later born cohort will show better levels of cognitive performance and slower rate of cognitive decline than the earlier born cohort, and that educational attainment will account for cohort differences in levels of cognitive performance and rates of cognitive decline.

Cross-sectional associations between cognitive abilities and depression symptoms dimensions

Depression tends to co-occur with cognitive impairment in late life, but the extent to which specific depression symptom dimensions may show differential associations with cognitive dysfunctions is unclear. Emerging evidence suggests that motivational and somatic symptoms of depression may be more strongly associated with cognitive dysfunctions than mood symptoms. To address this research question there is a need for psychometric work aimed at disentangling depression symptom dimensions underlying a depression measure. Moreover, there is a need to ensure

that depression dimensions are assessed in the same way across various groups of interest (e.g., countries, age, gender, cognitive functioning levels). This is achieved by ensuring that individuals with the same latent trait score do not differ in their item response behaviour, or that any differences in item response behaviour due to group membership are adjusted for. For instance, in the absence of genuine difference in depression, males may under-report crying spells (Carleton et al., 2013; Yang & Jones, 2007), older persons may under report dysphoria (Gallo et al., 1994; Gallo, Rabins, & Anthony, 1999), and persons with poorer cognitive functioning may over-report concentration difficulties and energy loss (Fieo et al., 2015). Adjusting for differences in item response behaviour due to age, gender and cognitive functioning levels would ensure that substantive conclusions regarding the association between depression dimensions and cognitive abilities are not affected by these potential biases in item responses.

Findings on the differential association between depression symptom dimensions and various cognitive domains are scarce and inconsistent. However, based on emerging evidence, I hypothesise that motivational and somatic symptoms of depression will show stronger associations with cognitive dysfunctions than mood symptoms, and that these associations would persist after adjusting for differential item functioning due to country of origin, age, gender and cognitive function levels.

Longitudinal bidirectional associations between cognitive abilities and depression symptoms/symptom dimensions

The longitudinal association between cognitive dysfunctions and depression symptoms remains unclear, with some studies reporting that higher initial

depression symptoms predict steeper cognitive decline, and some other studies reporting the opposite direction of the effect whereby poorer initial cognitive functioning predicts a higher increase in depression symptoms over time. This leaves an unresolved question of whether depression is a risk factor for cognitive decline, a psychological reaction to perceived cognitive deficits, or a prodromal syndrome of dementia. To overcome problems of reverse causation, there is a need for methods that can disentangle the direction of the effect by examining bidirectional prospective associations as well as synchronous longitudinal associations between depression symptoms and cognitive performance.

Moreover, there is a need to examine the extent to which longitudinal patterns of association between depression symptoms and cognitive functioning depend on the depression symptom dimensions experienced. For instance, affective symptoms of depression may be more dominant in the early stages of cognitive impairment and may manifest as a psychological reaction to perceived cognitive failures, whereas somatic and motivational symptoms of depression may be associated with a more chronic course of cognitive decline.

Consistent with the hypothesis that depression symptoms are a risk factor for cognitive impairment, I expect that higher initial depression scores would predict steeper cognitive decline over time. Based on emerging evidence, I expect this effect to be stronger for somatic and/or motivational symptoms of depression than for mood symptoms. Consistent with the hypothesis that depression symptoms develop as a psychological reaction to cognitive dysfunctions, I expect that poorer initial cognitive performance would predict an increase in depression symptoms over time,

and that this effect would be stronger for mood symptoms than for somatic and/or motivational symptoms of depression. Consistent with the hypothesis that depression and cognitive dysfunctions share a similar aetiology (e.g., dementia-related neuropathological burden, cerebrovascular diseases), I expect a synchronous association between increasing depression symptoms and declining cognitive performance over time. Based on the emerging evidence suggesting that somatic/motivational symptoms of depression may be related to a chronic course of cognitive decline, I expect increasing somatic/motivational symptoms to correlate more strongly with declining cognitive function over time than mood symptoms. These hypotheses are not mutually exclusive and their simultaneous examination could help clarify the effect magnitude and direction of influence between cognitive abilities and late-life depression dimensions. Moreover, the examination of these hypotheses in studies with different follow-up durations could inform on the timing of the association between depression symptoms/symptom dimensions and cognitive functioning.

1.7 Thesis structure

Chapter 1 introduces background issues, reviews the extant literature, highlights key concepts, and outlines the scope of the research.

Chapter 2 describes the cohort characteristics of the data analysed in this thesis using study samples from the 10/66 Dementia Research Study and the Longitudinal Ageing Study Amsterdam (LASA). This chapter includes a description of the study sample, the follow-up assessments, the data collection procedure, the attrition rates and reasons for drop out, as well as the strengths and limitations of these studies.

Furthermore, this chapter describes in greater detail the analytic approaches employed: Confirmatory Factor Analysis (CFA), Multiple Indicators Multiple Causes Models (MIMIC), Linear Mixed Models (LMM), Cross-Lagged Path Analysis, Univariate and Cross-domain Latent Growth Curve Models (LGCM).

Chapter 3 reports on differences in cognitive performance and rates of decline between earlier born and later-born cohorts, and discusses the role of educational attainment in accounting for these cohort effects in a Dutch sample of older adults who participated in the LASA study. This chapter is presented as a published paper and it is the exact copy of the following journal publication:

Brailean, A., Huisman, M., Prince, M., Prina, A. M., Deeg, D. J. H., & Comijs, H. (2016). Cohort Differences in Cognitive Aging in the Longitudinal Aging Study Amsterdam. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences.*, Advance online publication. doi:10.1093/geronb/gbw129

Chapter 4 reports on findings from a psychometric study which examined: a) the factor structure of the Centre for Epidemiologic Studies Depression Scale (CES-D); b) differential item functioning due to age, gender, and cognitive function levels; c) cross-sectional associations between latent dimensions of depression and various cognitive abilities in a sample of Dutch older adults (LASA study). This chapter is presented as a published paper and it is the exact copy of the following journal publication:

Brailean, A., Comijs, H. C., Aartsen, M. J., Prince, M., Prina, A. M., Beekman, A., & Huisman, M. (2016). Late-life depression symptom dimensions and cognitive

functioning in the Longitudinal Aging Study Amsterdam (LASA). *J Affect Disord*, 201, 171-178. doi:10.1016/j.jad.2016.05.027

Chapter 5 reports on findings from a psychometric study which examined: a) the factor structure of the Euro-D depression scale; b) its invariance across Latin American countries; c) differential item functioning due to age, gender, and cognitive function levels; d) cross-sectional associations between latent dimensions of depression and various cognitive abilities in older adults from six Latin American countries (10/66 study). This chapter is presented as a published paper and it is the exact copy of the following journal publication:

Brailean, A., Guerra, M., Chua, K. C., Prince, M., & Prina, M. A. (2015). A multiple indicators multiple causes model of late-life depression in Latin American countries. *J Affect Disord*, 184, 129-136. doi:10.1016/j.jad.2015.05.053

Chapter 6 reports on the longitudinal bidirectional associations between depression and various cognitive abilities in a sample of Dutch older adults who participated in the LASA study. Associations with cognitive functioning are investigated using depression as a unitary construct, as well as specific symptom dimensions previously established through factor analysis. This chapter is presented as a published paper and it is the exact copy of the following journal publication:

Brailean, A., Aartsen, M. J., Muniz-Terrera, G., Prince, M., Prina, A. M., Comijs, H. C., . . . Beekman, A. (2016). Longitudinal associations between late-life depression dimensions and cognitive functioning: a cross-domain latent growth curve analysis. *Psychological Medicine*, 1-13. doi:10.1017/S003329171600297X

Chapter 7 reports on the longitudinal bidirectional associations between depression symptoms and various cognitive abilities in a sample of older adults from six Latin American countries who participated in the 10/66 Dementia Research Study. Associations with cognitive functioning are investigated using depression as a unitary construct, as well as specific symptom dimensions previously established through factor analysis.

Chapter 8 summarises the research findings, discusses the insights obtained from the research investigations conducted, describes the strengths and limitations of the studies, as well as the implications for research, public health and clinical services.

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CHAPTER 2. METHODS

The research investigations conducted for this thesis were based on secondary data analysis using the 10/66 Dementia Research dataset in six Latin American countries and the Longitudinal Aging Study Amsterdam (LASA) dataset in the Netherlands. In this chapter I describe the study aims, the data collection procedure, the attrition rates and reasons for drop out, as well as the strengths and limitations of the studies. Furthermore, I present the analytic approaches employed in this thesis: Linear Mixed Models, Confirmatory Factor Analysis, Multiple Indicators Multiple Causes Models, Univariate and Cross-Domain Latent Growth Curve Models, Cross-Lagged Path Analysis.

2.1 Sample description - The Longitudinal Aging Study Amsterdam (LASA)

2.1.1 Aims

The Longitudinal Aging Study Amsterdam is an ongoing study initiated by the Dutch Ministry of Health, Welfare and Sport in 1991 to examine physical, emotional, social and cognitive functioning in late life. The study aims to understand how these components of functioning are interrelated, how they change over time, and what the determinants and consequences of these changes are. A detailed description of the cohort profile and the design of the LASA study have been previously published elsewhere (Hoogendijk et al., 2016; Huisman et al., 2011).

2.1.2 Data collection

Data were obtained from 11 municipalities across three culturally distinct regions in the Netherlands (i.e., Amsterdam, Zwolle and Oss) with the aim of ensuring a fair representation of urban and rural populations and of the main

religious groups (i.e., protestant, catholic and secular) in the Netherlands. An initial cohort (N = 3107) of respondents aged 55-84 years old (born in 1908-1937) received the baseline assessment in 1992-1993. The response rate for baseline assessments was 85%. This initial cohort was followed up every three years in 1995-1996, 1998-1999, 2001-2002, 2005-2006, 2008-2009, and 2011-2012. A second cohort (N = 1002) of respondents aged 55-64 (born in 1938-1947) undertook an initial assessment in 2002-2003, and was followed up in 2005-2006, 2008-2009, and 2011-2012. A third cohort (N = 1023) of respondents aged 55-64 (born in 1948-1957) was first assessed in 2012-2013. Additional assessments are being conducted in 2015-2016 in all three cohorts.

Assessments were conducted in participants' homes by trained interviewers. Participants signed an informed consent for participating in the study. The main interview lasted approximately 1 hour and 45 minutes. At the end of the main interview, participants were asked permission for a medical interview to be conducted in a separate visit. Those who provided consent to participate in the medical interview were administered additional clinical measures.

2.1.3 Data used in this thesis

Table 3 presents the samples included in each study and the reasons for selecting the respective samples. Data from LASA are used in Chapter 3, Chapter 4 and Chapter 6.

The investigation presented in Chapter 3 (i.e., including an investigation of cohort differences in cognitive ageing) uses data from the first LASA cohort (waves C, D and E) and the second LASA cohort (waves E, F, and G) from participants aged

65 to 75 at baseline. This age range is used to ensure that repeated measures of all cognitive abilities were available for two distinct birth cohorts (i.e., the first cohort was born in 1920 – 1930; the second cohort was born in 1931 - 1941).

The investigation presented in Chapter 4 (i.e., including an examination of the factor structure of the CES-D depression scale, differential item functioning due to age, gender and cognitive function levels, and associations between depression symptom dimensions and cognitive abilities) uses data from the first LASA cohort (wave B) from participants aged 55-85 years old ($N = 3107$). This data cycle was preferred because it included a larger sample size and a smaller amount of missing data.

The investigation presented in Chapter 6 (i.e., including an investigation of longitudinal bidirectional associations between depression symptoms/symptom dimensions and cognitive abilities) uses data from the first LASA cohort (waves C, D, E, F, and G) from participants aged 65 to 89 years old ($N = 1506$). These data cycles were selected in order to ensure a relatively long duration of the follow-up (13 years), and a large proportion of data present at baseline on all measures (over 90%).

As the studies presented in each chapter include different LASA cohorts and subsamples, I present descriptive statistics within each chapter.

2.1.4 Attrition rates

Attrition rates and the reasons for dropout based on the overall LASA sample are presented in Figure 1. Mortality accounted for most of the dropout cases, which is a common finding in longitudinal ageing studies. Other reasons for dropout

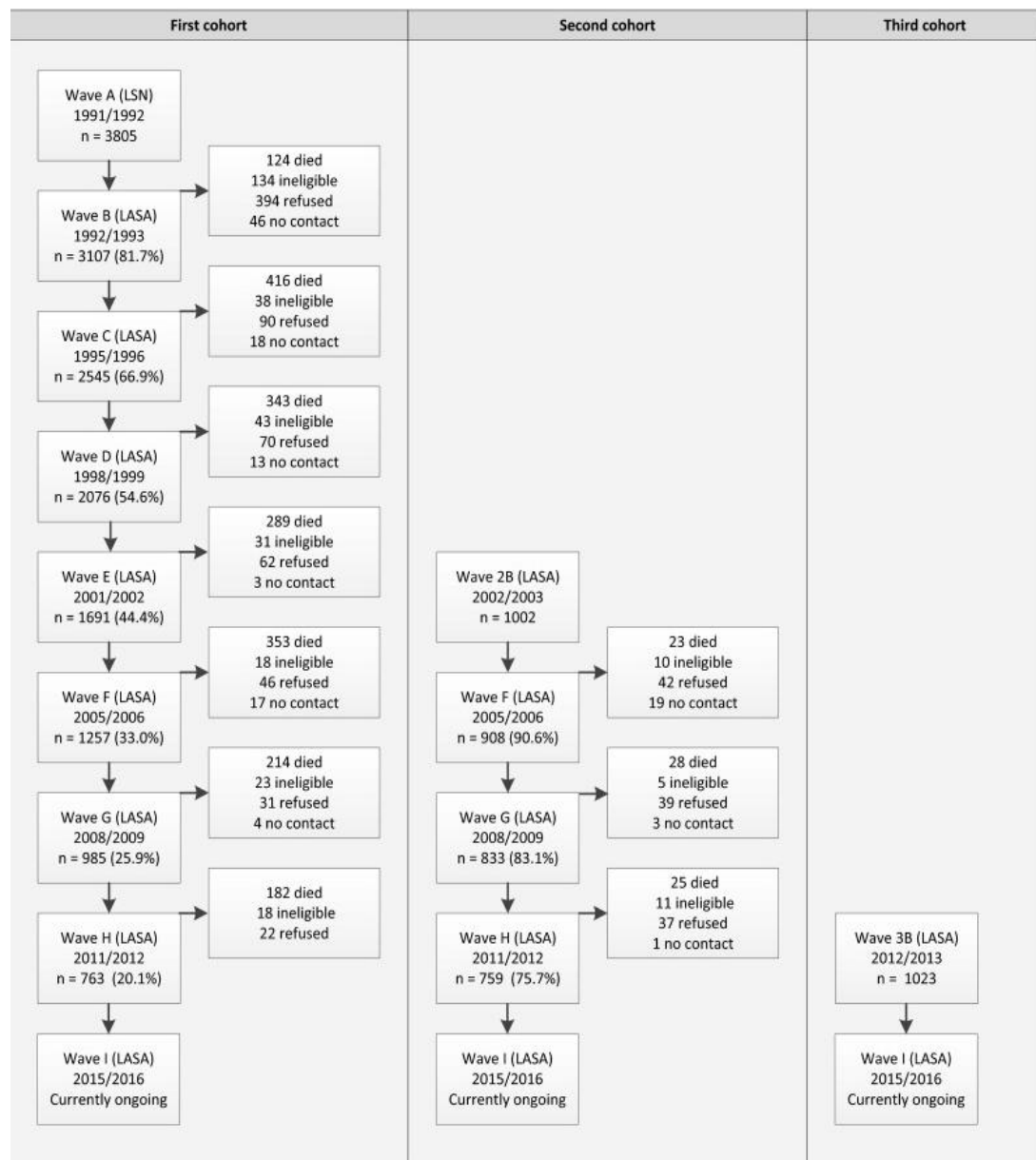
included refusal to participate, ineligibility (due to frailty), and lack of contact. Higher dropout rates were associated with being male, having lower educational attainment, having a higher number of chronic diseases, as well as potential cognitive impairment (i.e., a score of 23 and below on the Mini Mental State Examination), and potential clinical depression (a score of 16 and above on the CES-D depression scale) (Huisman et al., 2011).

As the longitudinal studies presented in Chapter 3 and Chapter 6 include different LASA subsamples, the attrition rates, reasons for dropout and predictors of dropout are described in the respective chapters.

2.1.5 Strengths and limitations

Strengths of the LASA study are the inclusion of a large sample of older adults, the inclusion of multiple measures for a wide array of functioning components, the cohort sequential design allowing for an examination of cohort differences in various areas of functioning, and the repeated follow-up assessments spanning over a relatively long period. A potential limitation of the LASA study is the interval of 3 years between measurements which may be too long to capture relevant changes in certain functioning domains (e.g., depression). Another limitation is the high attrition rate (largely due to mortality) and the selective dropout of less healthy participants, which may bias findings regarding the association between various components of functioning.

Figure 1. LASA measurement cycles



Source: Hoogendijk et al. (2016)

2.2 Sample description - The 10/66 Dementia Research Study

2.2.1 Aims

The 10/66 Dementia Research Study is a study of health and ageing that aimed to bridge the research gap of dementia research in low and middle income countries (LMIC). The study is called 10/66 to reflect the fact that when the 10/66 Dementia Research group was formed, it was estimated that less than 10% of the population-based research on dementia was carried out in LMIC, despite the fact that 66% of persons with dementia were living in LMIC. The 10/66 study aimed to develop dementia diagnosis instruments that are culture and education fair, and to examine the prevalence and incidence of dementia in LMIC. The 10/66 study included also assessments of mental and physical disorders, anthropometry, demographics, risk factors for non-communicable diseases, disability, health service utilisation, and care arrangements (Prina et al., 2016; Prince et al., 2007). Studies were approved by local ethical committees in each country, and by the King's College London Research Ethics Committee.

2.2.2 Data collection

Baseline surveys were conducted in catchment areas from Latin American countries (i.e., Cuba, Brazil, Dominican Republic, Venezuela, Mexico, Peru, Puerto Rico), China and India. Included participants were aged 65 and above at the moment of the baseline assessments, which were carried out between 2007 and 2009 in Puerto Rico, and between 2003 and 2006 in all the other countries. Geographically defined catchments areas were selected in each country based on a sample size between 2000 and 3000, and taking into account criteria such as accessibility, and

opportunities to involve local research groups and community stakeholders. Both urban and rural catchment areas were selected in Peru (Lima – urban; Canete Province - rural), Mexico (Mexico City – urban; Morelos State - rural), and China (Xicheng, Beijing Province – urban; Daxing, Beijing Province - rural), whereas only urban catchment areas were selected in Cuba (Havana and Matanzas), Dominican Republic (Santo Domingo), Puerto Rico (Bayamon), Venezuela (Caracas), and India (Chennai). Rural catchment areas were characterised by agrarian lifestyle and low population density, whereas urban catchment areas were characterised by high population density and low socioeconomic status. Households within each of these catchment areas were given an identification number. Following door-knocking, participants aged 65 and above were considered eligible for the study. They were given an identification number and were asked to sign an informed consent before the interview. Illiterate participants provided oral consent in the presence of a witness. Interviews were conducted in participants' homes by trained interviewers and lasted about 2-3 hours. All the instruments were administered in the native language of participants. All centres showed good response rates for the baseline survey, ranging from 72% to 98%. Follow-up assessments were conducted 3-4 years after the baseline assessment (between 2012 and 2013 in Puerto Rico and between 2007 and 2010 in all other centres). New follow-up assessments are being conducted in 2016-2017 in Latin American countries and China.

2.2.3 Data used in this thesis

Table 3 includes a brief description of the samples included in each study and the reasons for selecting the respective samples. Data from the 10/66 study were used in Chapter 5 (i.e., including a cross-sectional examination of the factor structure of

EURO-D, differential item functioning due to country of residence, age, gender, and cognitive function levels, and associations between depression symptom dimensions and cognitive abilities), and Chapter 7 (i.e., including a longitudinal investigation of longitudinal bidirectional associations between depression symptoms/symptom dimensions and cognitive abilities). The studies presented in Chapter 5 and Chapter 7 included only participants who were living in Latin American countries (Peru, Venezuela, Mexico, Puerto Rico, Cuba, Dominican Republic), who were aged 65 and above, and who had no diagnosis of dementia at baseline (see Figure 2). Study participants from India were excluded because only those who had dementia or cognitive impairment at baseline were followed up in this country. Persons from China were excluded because they had a low prevalence of depression, possibly reflecting a tendency to under-report depression symptoms due to cultural biases and stigma related to mental health disorders. Previous 10/66 studies reported a mean Euro-D score of 0.5 in urban China and 0.2 in rural China (Guerra, Ferri, Llibre, Prina, & Prince, 2015). This is much lower than the mean Euro-D scores reported by the 10/66 study in Latin American countries (ranging between 2.1 in Cuba and 3.0 in Dominican Republic) and India (3.2) (Guerra et al., 2015), and by the EURODEP study and the SHARE study in European countries (ranging from 1.8 in Denmark to 3.1 in Spain) (Castro-Costa et al., 2007, 2008). The study presented in Chapter 5 excluded persons with a diagnosis of dementia at baseline because of concerns that the subjective reports of mood symptoms may be inaccurate and that the validity of the depression factor structure may be altered in persons with dementia. Similar concerns formed the basis for excluding persons with baseline dementia from the longitudinal study presented in Chapter 7. An additional concern in the longitudinal

study presented in Chapter 7 was that persons with a diagnosis of dementia at baseline may be in the severe stages of dementia at follow-up, which would limit the validity of their responses to both cognitive and depression measures. Follow-up data from all participants who were dementia-free at baseline was included, regardless of whether they developed dementia at follow-up or not. This decision was motivated by the fact that I was interested in cognitive change and excluding those who developed dementia at follow-up would have reduced the spectrum of cognitive decline observed and the generalisability of findings. Moreover, because persons who were free of dementia at baseline were unlikely to have progressed towards severe dementia at follow-up, including them would not likely severely affect the validity of their responses.

Table 1 presents descriptive statistics for the study sample in each country: age, gender, education (none, some primary, completed primary, completed secondary, completed tertiary), occupation (highest level job ever had: professional, trade, skilled labour, labour), number of household assets (fridge, television, telephone, water, electricity, plumbed toilet, plumbed bathroom), food insecurity (i.e., Do you ever go hungry because there is not enough food to eat?), and number of physical impairments (self-reported limb weakness, eyesight problems, gastrointestinal problems, arthritis, heart problems, hypertension, hearing difficulties, respiratory problems, faint or blackouts, skin disorders, persistent cough).

Table 1. Baseline characteristics of the 10/66 sample by country

Variable	Cuba		Dominican R.		Peru		Venezuela		Mexico		Puerto Rico		Overall	
	N	M	N	M	N	M	N	M	N	M	N	M	N	M
Age	2511	74.4	1769	74.5	1767	74.2	1819	72	1823	73.7	1765	75.4	11454	74.0
Female	N.	%	N.	%	N.	%	N.	%	N.	%	N.	%	%	N.
	1628	64.7	1156	65.4	1073	60.7	1150	63.2	1144	62.8	1183	67.2	7334	64.0
Education														
None	54	2.2	315	17.9	103	5.9	133	7.4	461	25.3	47	2.7	1113	10.2
Some primary	522	20.8	917	52.0	212	12.1	408	22.6	802	44.0	313	17.8	3174	28.2
Completed primary	829	33.0	338	19.2	654	37.2	913	50.5	337	18.5	356	20.2	3427	29.8
Completed secondary	661	26.3	126	7.2	486	27.7	262	14.5	117	6.4	661	37.6	2313	20.0
Completed tertiary	446	17.8	66	3.8	301	17.1	92	5.1	104	5.7	383	21.8	1392	11.9
Number of assets														
0-2	25	1	110	6	35	2	33	2	192	11	4	<1	399	4.4
3-5	843	34	831	47	382	22	9	0	607	33	32	2	2704	23.0
6-7	1642	65	823	47	1350	76	1778	98	1024	56	1729	98	8346	73.3
Occupational class														
Professional	966	40.6	301	17.1	614	35.2	592	35.2	228	12.5	915	52.0	3616	32.1
Trade	328	13.8	235	13.3	278	15.9	406	24.1	205	11.3	397	22.6	1849	16.8
Skilled labour	676	28.4	690	39.2	440	25.2	605	35.9	566	31.1	343	19.5	3320	29.9
Labour	408	17.2	535	30.4	412	23.6	81	4.8	824	45.2	105	6.0	2365	21.2
Food insecurity	120	4.8	207	11.8	132	7.5	108	6.2	110	6.1	22	1.3	699	6.3
Physical impairments														
0	1100	43.8	537	30.4	826	46.8	719	39.6	789	43.3	644	36.6	4615	40.1
1 or 2	1167	46.4	842	47.7	713	40.4	650	35.8	740	40.6	776	44.1	4888	42.5
3 or more	246	9.8	388	22.0	227	12.9	446	24.6	294	16.1	340	19.3	1941	17.5

2.2.4 Attrition rates

The attrition rates for our study sample (i.e., participants from Latin American countries free of dementia at baseline) are presented in Table 2. The overall loss at follow-up was 30 % for the overall sample, ranging between 39% in Dominican Republic and 23 % in rural Peru and urban Mexico. The main reason for dropout was mortality which accounted for 41% of dropout cases across countries. With the exception of Puerto Rico, information was available in all countries about the number of participants who were followed up, those who died, those who refused to participate, those who were not traced (i.e., it could not be established where they lived at the moment of the follow-up), and those who were not contactable (i.e., participants who were traced but who did not respond to door knocking). In Puerto Rico information was recorded about the number of participants who were not followed up because of death, but other reasons for the absence of follow-up data were not available (i.e., refusal, not traceable, not contactable).

2.2.5 Strengths and limitations

Strengths of the 10/66 study include the relatively large sample size, the use of education-fair cognitive measures, the high response rate and the relatively low amount of missing data. One of the limitations of this study is that the recruitment of participants from specific catchment areas may have limited the generalisability of the findings. Also, the accuracy of participants' responses may have been affected by the fact that interviews were conducted in their own homes which were sometimes noisy and overcrowded.

Figure 2. Cohort diagram of the baseline and follow-up 10/66 surveys for dementia-free participants in Latin American countries

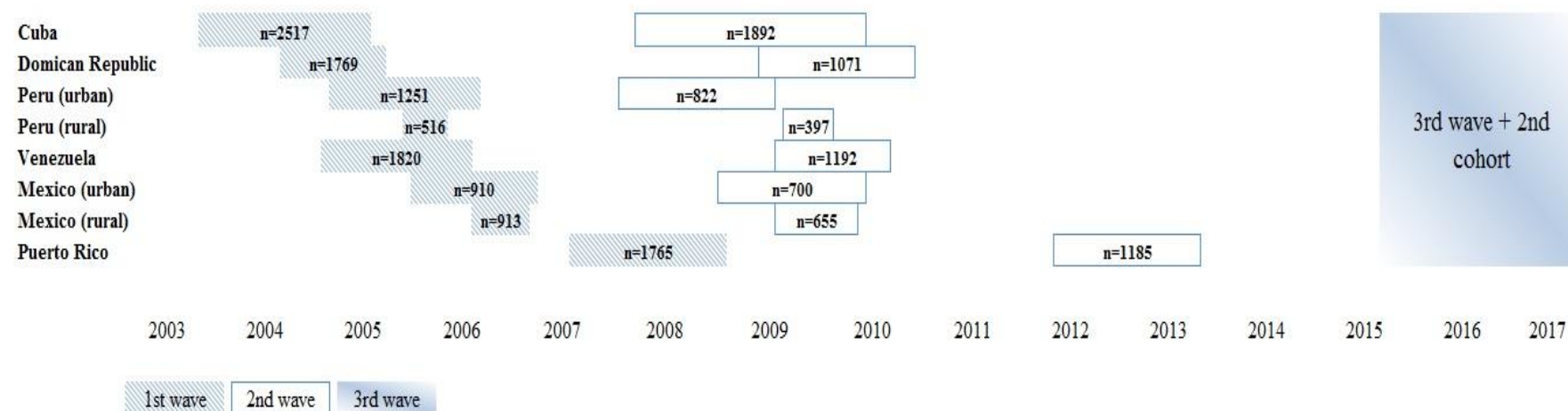


Table 2. Attrition rates in the 10/66 study for dementia-free participants in Latin American countries

Country	Followed	Dropout					Total
		Died	Refused	Uncontactable	Not traced	Not recorded	
Cuba	1,892	449	17	119	40	0	2,517
DR	1,071	370	41	54	233	0	1,769
Peru (urban)	822	61	248	46	74	0	1,251
Peru (rural)	397	48	30	24	17	0	516
Venezuela	1,192	161	221	238	0	8	1,820
Mexico (urban)	700	78	57	56	19	0	910
Mexico (rural)	655	88	106	44	20	0	913
Puerto Rico	1,185	200	6	11	30	333	1,765
Total	7,914	1,455	726	592	433	341	11,461

2.3. Analysis methods

2.3.1 Linear Mixed Models

Linear Mixed Models were used in Chapter 3 in the investigation of cohort differences in cognitive ageing. Linear Mixed Models consist of fixed effects (e.g., the effect of cohort on cognitive scores) and random effects which can account for correlated data such as the dependency of repeated measurements of a target outcome within the same individuals over time. Linear Mixed Models can handle missing data using maximum likelihood (ML) estimation under the missing at random (MAR) assumption, by calculating parameters using both cases with complete data and cases with partially missing data (for a description of the missing data mechanisms see section 2.4).

2.3.2 Confirmatory Factor Analysis

Confirmatory factor analysis (CFA) was used in Chapter 4 and Chapter 5 to establish the factor structure of the CES-D and Euro-D depression scales. CFA models can be thought of as a theory-testing approach allowing to test predetermined models that specify the number and composition of latent factors. In a CFA context latent variables (i.e., hypothetical constructs) are inferred from other variables that are measured/observed (i.e., item responses). The correlation between the latent variable and the measured variable is reflected in a regression coefficient termed “factor loading”. The latent variable/construct is assumed to explain the covariance between certain items (e.g., the fact that someone has high verbal scores and high quantitative scores may suggest that person is intelligent; intelligence is a latent construct inferred from someone’s relatively high scores on certain cognitive tests).

A priori hypotheses are tested by fixing or freeing specific parameters, such as the factor loadings or the correlations between latent variables, and models are tested against the data to establish the extent to which model predictions match the observed data. This match between model and data can be summarised by a family of fit indices. Models with poor indices of fit are rejected.

Several variations of CFA exist, including first-order CFA, second order CFA, and bi-factor CFA. A first order CFA model hypothesizes that a number of latent factors explain the covariance between specific depression items. An example of first-order CFA model is illustrated in Figure 3, representing the factor structure of the CES-D depression scale used in Chapter 4. This model consists of four factors: depressed affect (measured by 7 items), somatic symptoms (measured by 7 items), positive affect (measured by 4 items), and interpersonal difficulties (measured by 2 items). Single headed arrows from the latent factor to the indicators represent factor loadings, or the extent to which the latent factor influences responses to certain items. Latent factors in the model are assumed to be correlated, and their correlation is illustrated by double headed arrows. The measurement errors displayed in grey reflect the unique variance of each item that is not explained by the latent factor. It is assumed that measurement errors are uncorrelated among themselves and uncorrelated with the latent factors.

My thesis used the original first-order factor models of the CES-D and Euro-D depression scales which were previously validated in factor analytic studies of these depression scales. The use of first-order CFA served my aims of investigating the relation between specific depression symptom dimensions and cognitive abilities,

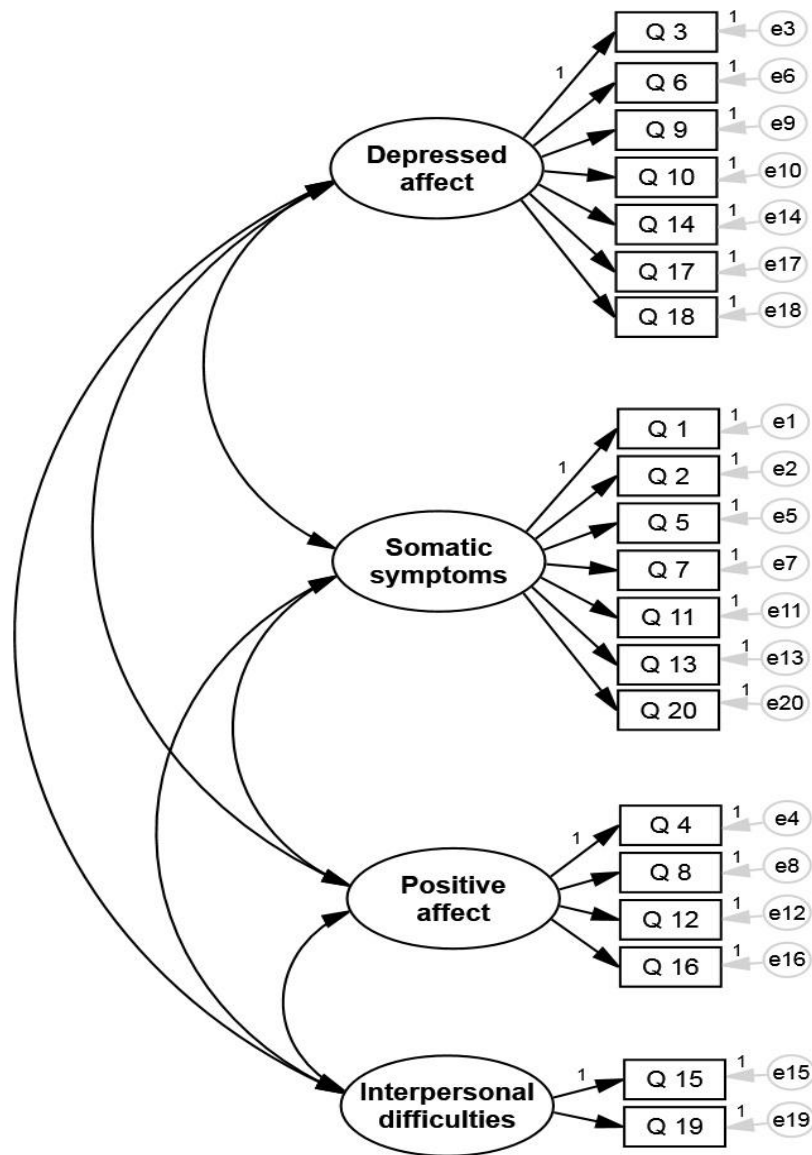
while adjusting for differential item functioning effects that operate at the level of the specific depression dimensions. These aims were achieved using Multiple Indicators Multiple Causes Models (MIMIC) which incorporate a first-order CFA model (for a description of MIMIC models please refer to section 2.3.3).

Although the original factor structure of these depression scales has been widely used in previous studies, alternative factor solutions have been proposed, including second-order factor models, and bi-factor models. A second-order CFA model hypothesizes a general factor that explains the common variance in the first-order factors (e.g., depressed affect, positive affect, somatic symptoms interpersonal difficulties). Both the first-order factor models and the second order-factor models hypothesize that latent depression factors are correlated, but this correlation among first-order factors is only modelled as a general factor in the context of second-order factor models. In a second-order model, differences in latent means and differential item functioning between groups can only be tested at the level of the general factor, because the first-order factors are represented by disturbances (Chen, West, & Sousa, 2006). This is one of the reasons why first-order factor models were preferred in my studies.

Unlike second-order CFA models, bi-factor CFA models hypothesize a general factor which explains the common variance in all items (“depression” construct), and which is uncorrelated (i.e., orthogonal) with specific factors (i.e., depressed affect, positive affect, somatic symptoms interpersonal difficulties). The specific factors explain additional variance in specific items that is not fully captured by the general factor. Bi-factor models have the advantage that specific

factors can be tested for associations with external covariates and for DIF between groups. However, due to the orthogonality constraint, the bi-factor model assumes that the specific factors are independent from “depression” (i.e., uncorrelated with the general factor), as well as independent among themselves (because allowing specific factors to correlate would imply the existence of additional general factors). The interpretation of specific factors may be challenging, partly due to the orthogonality constraint (i.e., If specific factors do not measure “depression”, what do they measure?), and partly due to the composition of the specific factors (i.e., specific factors may emerge as method effects reflecting spurious correlations between items rather than theoretically meaningful constructs).

Figure 3. Confirmatory Factor Analysis



Note: Example of a first-order CFA model showing 4 correlated latent dimensions of the CES-D depression scale, each measured by several depression items (Q1 to Q20). The model also estimates the measurement errors for each item (e1 to e20). Circles are used to represent latent variables (i.e. depression factors). Squares are used to represent measured variables (i.e., item responses).

2.3.3 Multiple Indicators Multiple Causes Models (MIMIC)

MIMIC models were used in Chapter 4 and Chapter 5 for investigating associations between late-life depression dimensions and cognitive abilities in the context of adjustment for differential item functioning. A MIMIC model is essentially a CFA model with covariates and it can be used to investigate the association between covariates and latent constructs (i.e., factors), as well as between covariates and item responses (see Figure 4).

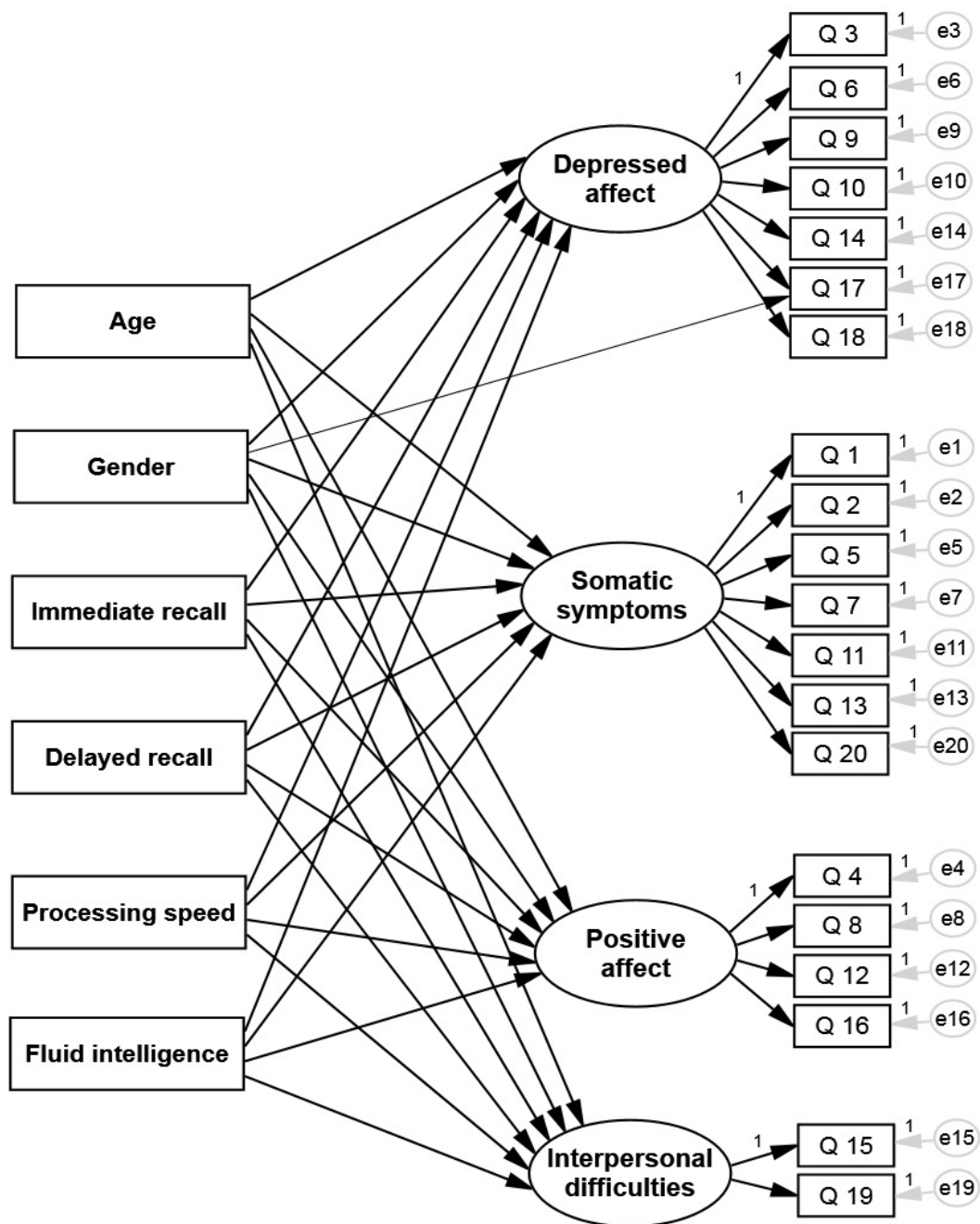
The MIMIC model consists of the following components:

- a) a CFA model specifying the relation between items and latent factors;
- b) a regression model specifying the associations between covariates and latent factors, which informs on group differences in factor means (e.g., women score higher on “depressed affect” than males);
- c) a regression model specifying the associations (also referred to as “direct effects”) between covariates and items; this part of the model informs on differences in item responses due to group membership, in the context of adjustment for the mean latent scores (e.g., accounting for gender differences in levels of depressed affect, males have a lower probability of responding “Yes” to the item “Have you cried at all?”). The presence of direct effects indicates measurement non-invariance or differential item functioning (DIF).

The estimation of a MIMIC model typically starts by validating the factor structure of the underlying constructs at the CFA stage. After establishing the factor structure, covariates are added to the model and their association with latent constructs is investigated. Moreover, the model examines the extent to which item

responses differ according to the level of specific covariates (i.e., DIF effects). Statistically significant DIF effects are added to the model in a step-wise manner. If DIF effects are of small magnitude and their estimation does not change conclusions about the association between covariates and latent constructs, it is considered that the latent constructs are measured in a similar way across levels of the covariates and that measurement invariance is achieved. Conversely, the factorial validity of the model is undermined if DIF effects are significant and of high magnitude, and if their estimation changes conclusions regarding the association between covariates and latent constructs.

Figure 4. Multiple Indicators Multiple Causes Model

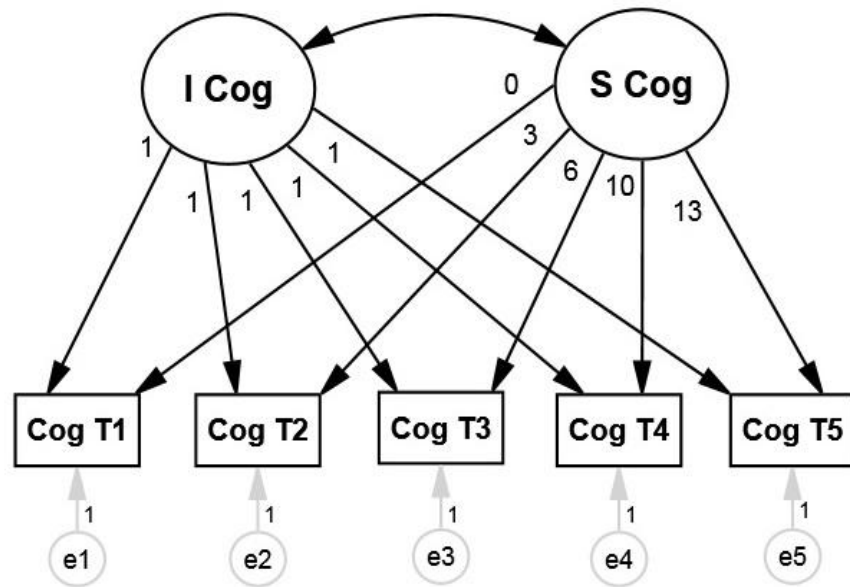


Note: MIMIC model showing the impact of age, gender and cognitive abilities on the CES-D measurement model with four factors. Only one example of DIF effect is illustrated, indicating gender differences in the probability of endorsing the CES-D item 17 (crying spells).

2.3.4 Univariate Latent Growth Curve Models (LGCM)

Univariate LGCM were used in Chapter 6 to examine the trajectories of depression and cognitive abilities (see Figure 5). Univariate LGCM allow to examine a) the mean initial value of the outcome (i.e., mean intercept); b) individual differences in the initial value of the outcome (i.e., intercept variance); c) the rate of change in the outcome (i.e., mean slope) and its form (e.g., linear, quadratic); d) individual differences in the rate of change in the outcome (i.e., slope variance); e) the association between the initial level of the outcome and the rate of change in the outcome (e.g., persons who start off with poorer cognitive performance show steeper cognitive decline over time); f) individual differences in the intercept and slope of the outcome as a function of various covariates (e.g., older participants show poorer initial cognitive performance as well as steeper rates of cognitive decline).

Figure 5. Univariate Latent Growth Curve Model



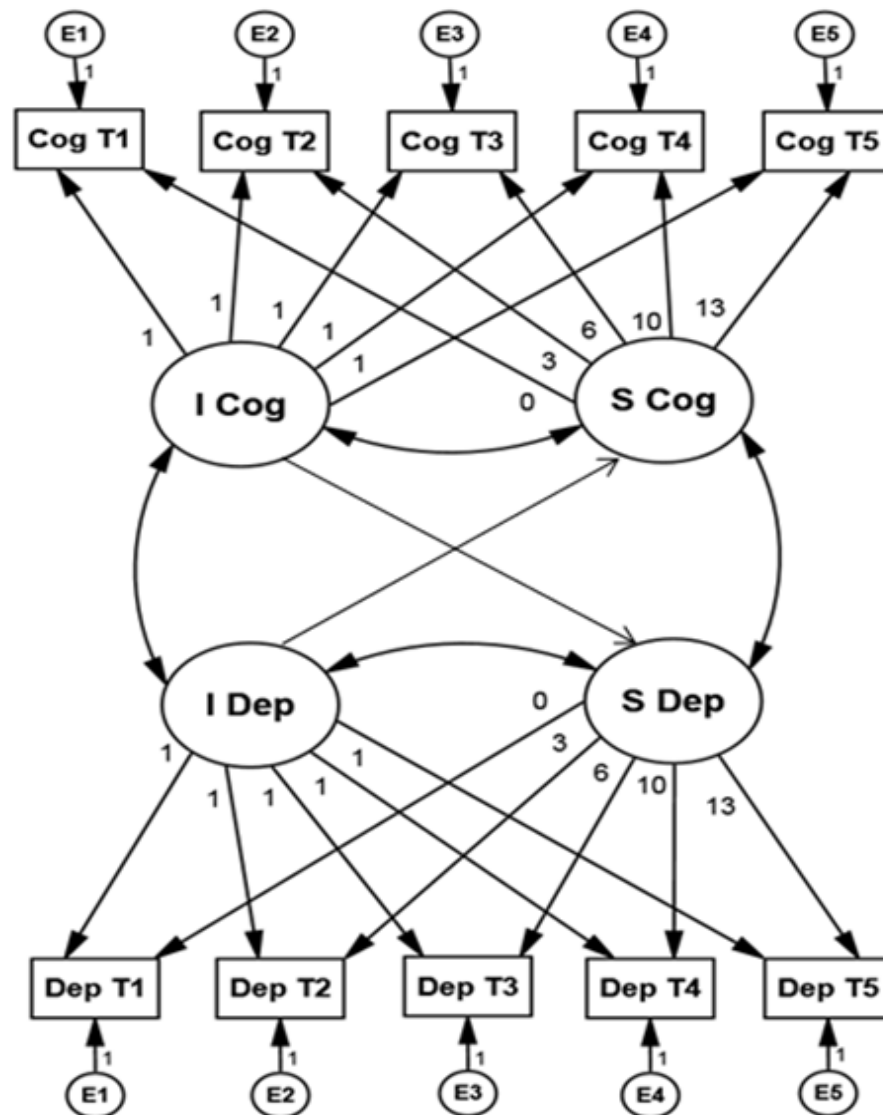
Note: Univariate LGCM illustrating the trajectory of cognitive functioning. I Cog refers to the intercept of cognition; S Cog refers to the slope of cognition. The double headed arrow represents the correlation between the intercept of cognition and the slope of cognition. The intercept factor loadings are fixed to a value of 1 to ensure that the model estimates baseline levels of cognitive functioning. The loadings of the measurements for the latent slope are set at 0, 3, 6, 10 and 13, representing changes in cognitive functioning over 13 years of follow-up (T1 to T5). The model assumes that all observed variables are influenced by random measurement error (e1 to e5).

2.3.5 Cross-Domain Latent Growth Curve Models (LGCM)

Cross-Domain LGCM were used in Chapter 6 to examine longitudinal associations between depression symptoms/symptom dimensions and cognitive abilities. Cross-domain LGCM can simultaneously model the growth process of multiple outcomes and the associations between outcomes (see Figure 6). On top of the parameters estimated in univariate LGCM models, cross-domain LGCM models estimate associations between: a) baseline levels of an outcome and baseline level of another outcome (e.g., correlation between baseline levels of depression and baseline levels of cognitive performance); b) baseline levels of an outcome and changes in another outcome (e.g., baseline levels of depression predicting changes in cognitive performance, and baseline levels of cognitive performance predicting changes in depression); c) the rate of change in an outcome being associated with the rate of change in another outcome (e.g., increasing depression levels being associated with declining cognitive performance over time).

Unlike cross-lagged models (discussed below), cross-domain LGCM can determine the shape of development over time (e.g., are changes in cognition/depression linear or quadratic) and it can examine the relation between changes in multiple processes (e.g., correlation between the slope of cognition and the slope of depression). A potential disadvantage of LGCM models is the lack of autoregressive parameters (which are included in cross-lagged models). LGCM models assume that the current value of each variable does not depend on its prior value and instead repeated measures of a variable are used to calculate the intercept and slope for each individual in the sample (Bollen & Curran, 2004).

Figure 6. Cross-Domain Latent Growth Curve Model



Note: Cross-domain LGCM illustrating the associations between depression and cognitive functioning. I Cog refers to the intercept of cognition; S Cog refers to the slope of cognition; The single headed arrow from I Cog to S Dep indicates that baseline levels of cognitive performance predict changes in depression. Similarly, the single headed arrow from I Dep to S Cog indicates that baseline levels of depression predict changes in cognition. Double headed arrows represent correlations. The intercept factor loadings are fixed to a value of 1 to ensure that the model estimates baseline levels of depression/cognitive functioning. The loadings of the measurements for the latent slope are set at 0, 3, 6, 10 and 13, representing changes in cognition/depression over 13 years of follow-up (T1 to T5). The model assumes that all observed variables are influenced by random measurement error (e1 to e5).

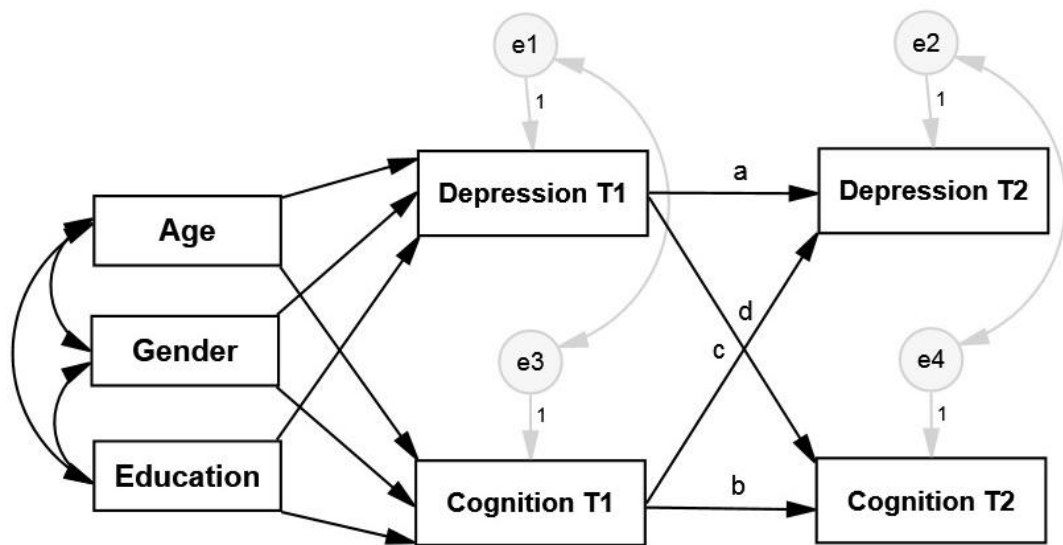
2.3.6 Cross-Lagged Path Analysis

Cross-lagged path models were used in Chapter 7 to investigate bidirectional associations between depression symptoms/symptom-dimensions and cognitive abilities. Cross-lagged models consist of stability paths, cross-lagged paths, and occasion-specific correlations (see Figure 7). Stability paths (also known as autoregressive effects) explain the stable part of individual differences (i.e., individuals who have high depression scores at baseline will tend to have high depression scores at follow-up). Cross-lagged effects explain the residual variability that is not explained by autoregressive effect (e.g., baseline depression levels predict follow-up cognition levels after accounting for baseline cognition levels). If only one cross-lagged regression coefficient is statistically significant this suggests a unidirectional effect. If both cross-lagged regression coefficients are statistically significant this suggests reciprocal influences between outcome measures (e.g., baseline depression predicts follow up cognition, and baseline cognition predicts follow-up depression). By estimating both directions of the effect in the same model it is possible to determine the relative magnitude of the predictive associations between outcomes (e.g., is the effect of baseline depression on follow-up cognition stronger than the effect of baseline cognition on follow up depression?). To account for shared occasion-specific effects, cross-lagged models also estimate correlations between outcomes at baseline and at follow-up.

It is believed that cross-lagged models are the most appropriate way of studying causality in the absence of an experimental design (Hamaker, Kuiper, & Grasman, 2015). An advantage of the cross-lagged path model relies in its ability to account for the temporal order of longitudinal data, whereby the current value of

each variable depends on its prior value. The single-step estimation of all model parameters allows to compare the standardized cross-lagged coefficients and determine the relative magnitude of each direction of the effect, while accounting for the stability of the constructs over time through the inclusion of autoregressive paths. Unlike LGCM models, cross-lagged path models cannot determine the shape of development over time (e.g., are changes in cognition/depression linear or quadratic). Moreover, cross-lagged path models use observed variables for depression and cognition which include some level of measurement error.

Figure 7. Cross-Lagged Path Analysis



Note: Paths a and b represent stability paths; paths c and d represent cross-lagged paths; models are adjusted for age, gender and education.

2.4 Handling missing data

Missing data mechanisms

Missing data is an ubiquitous challenge in longitudinal surveys. Three main mechanisms have been proposed for explaining the relationship between observed variables and the probability of missing data: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR) (see Figure 8) (Rubin, 1976).

The missing data mechanism is MCAR when there is no association between observed or unobserved variables and non-response (Rubin, 1976). It is assumed that data are missing due to a completely random phenomenon and that persons with complete records do not differ from persons with incomplete records in any respect. Therefore, inferences drawn based on the parameter estimates calculated for the sample with complete records would apply to the larger sample and the target population (Pigott, 2001). MCAR is a strict assumption which is rarely met in practical applications (Raghunathan, 2004).

A more relaxed assumption is MAR which posits that any systematic differences between the missing values and the observed values can be explained by observed data (i.e., variables assumed to drive the missingness). Given the observed data, missingness is not influenced by unobserved variables (Rubin, 1976).

When the missing data mechanism is MNAR systematic differences between the missing values and the observed values persist after accounting for all observed data; missingness is influenced by unobserved variables (Rubin, 1976).

When the missing data mechanism is MCAR or MAR, missing data is considered to be “non-informative” or “ignorable”. because missing data bias is not present or can be recovered from the information given by other variables. When the missing data mechanism is MNAR, missing data is considered “non-ignorable”. The MCAR assumption can be partially verified by testing whether observed variables in the dataset are predicting non-response. However, even if we fail to find an association between observed variables and non-response, it is not possible to test whether unmeasured variables (i.e., variables not included in the dataset) are influencing non-response. MAR and MNAR are unverifiable assumptions. However, conducting sensitivity analyses under the MAR assumption (e.g., using MLR estimation or multiple imputations) and under the MNAR assumption (e.g., pattern mixture models) can inform about the robustness of research conclusions to the effects of attrition under different missing data assumptions.

Missing data methods

Table 3 summarises the approaches used for handling missing data in each chapter.

Variance-Adjusted Weighted Least Squares Estimation (WLSMV) is considered to produce unbiased parameter estimates when the amount of missing data is not substantial and when data are assumed to be missing at random with respect to model covariates (Asparouhov & Muthen, 2014). WLSMV estimation was used in the studies presented in Chapter 4 and Chapter 5 because the percentage of missing data was low (under 5%) and the WLSMV estimation could facilitate model convergence.

Maximum Likelihood (ML) estimation is considered to produce unbiased parameter estimates under the MCAR and MAR assumptions (Pigott, 2001). This estimator calculates model parameters using both cases with complete data and cases with partially missing data. ML estimation (available in SPSS) was used in the longitudinal study presented in Chapter 3. Maximum Likelihood Robust (MLR) estimation (available in MPlus) was used in the longitudinal studies presented in Chapter 6 and Chapter 7. ML assumes multivariate normality, whereas MLR is robust to non-normality (Hox, Maas, & Brinkhuis, 2010).

Pattern mixture models can deal with missing data under the MNAR assumption. Pattern mixture models were used in Chapter 3 to test whether cohort differences in cognitive decline varied as a function of the missing data patterns (e.g., no dropout; dropout at time 1; dropout at time 2). This served as a sensitivity analysis to compare findings of cohort differences in cognitive decline under the MNAR assumption with findings from Linear Mixed Models with ML estimation under the MAR assumption. Additionally, the study presented in Chapter 3 included a comparison of the missing data patterns, the reasons for dropout and the predictors of dropout between cohorts.

Table 3. Study sample, analysis method and approach to missing data for each research investigation

Chapter/ Dataset	Sample	Reason for using this sample	Analysis method	Reason for using this method	Handling missing data
Chapter 3 LASA	Cohort 1: participants aged 65 to 75, born between 1920 and 1930 (N = 705); LASA waves C, D and E; Cohort 2: participants aged 65 to 75, born between 1931 and 1941 (N = 646); LASA waves F, G and H;	This age range was used to ensure that repeated measures of all cognitive abilities were available, and that there was no overlap between birth-cohorts across measurement waves.	LMM	LMM can account for the dependency of repeated measurements of a target outcome within the same individuals, and it can include cases with complete data or partially missing data.	ML estimation under the MAR assumption; Pattern mixture models under the MNAR assumption; Comparing the missing data patterns, reasons for dropout, and predictors of dropout between cohorts;
Chapter 4 LASA	Participants aged 55-85 (N = 3107); LASA wave B;	This data cycle included a larger sample size and a smaller amount of missing data.	MIMIC	MIMIC models can simultaneously estimate the factor structure of the depression scales, DIF effects, and associations between latent depression dimensions and cognitive abilities.	WLSMV estimation under the assumption that data are missing at random with respect to model covariates;
Chapter 5 10/66	Participants aged 65 and above without dementia (N = 10405); 10/66 wave 1;	The validity of the factor structure may be altered in persons with dementia.			
Chapter 6 LASA	Participants aged 65 and above (N = 1506); LASA waves C, D, E, F, G;	The aim was to ensure good data coverage on all measures (over 90% at baseline).	Cross-domain LGCM	LGCM can estimate bi-directional and synchronous longitudinal associations between cognition and depression.	MLR estimation under the MAR assumption;
Chapter 7 10/66	Participants aged 65 and above without dementia at baseline (N = 11461); 10/66 waves 1 and 2;	Persons with baseline dementia were excluded because they may progress to severe dementia during follow-up, which would limit the validity of their responses.	Cross-lagged path analysis	These models allow to estimate bidirectional longitudinal associations between depression and cognition.	MLR estimation under the MAR assumption;

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**CHAPTER 3: COHORT DIFFERENCES IN COGNITIVE AGEING IN THE
LONGITUDINAL AGING STUDY AMSTERDAM (LASA)**

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Original Research Report

Cohort Differences in Cognitive Aging in the Longitudinal Aging Study Amsterdam

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Abstract

Objectives: This study aims to examine cohort differences in cognitive performance and rates of change in episodic memory, processing speed, inductive reasoning, and general cognitive performance and to investigate whether these cohort effects may be accounted for by education attainment.

Method: The first cohort ($N = 705$) was born between 1920 and 1930, whereas the second cohort ($N = 646$) was born between 1931 and 1941. Both birth cohorts were aged 65 to 75 years at baseline and were followed up 3 and 6 years later. Data were analyzed using linear mixed models.

Results: The later born cohort had better general cognitive performance, inductive reasoning, and processing speed at baseline, but cohort differences in inductive reasoning and general cognitive performance disappeared after adjusting for education. The later born cohort showed steeper decline in processing speed. Memory decline was steeper in the earlier born cohort but only from Time 1 to Time 3 when the same memory test was administered. Education did not account for cohort differences in cognitive decline.

Discussion: The later born cohort showed better initial performance in certain cognitive abilities, but no better preservation of cognitive abilities overtime compared with the earlier born cohort. These findings carry implications for healthy cognitive aging.

Keywords: Aging—Cognitive abilities—Cognitive reserve—Cohort differences—Education

Aging is associated with a general decline in cognitive performance (Brayne et al., 1999; H. L. Park, O'Connell, & Thomson, 2003; Wilson, Beckett, Bennett, Albert, & Evans, 1999), which is especially pronounced for abilities that require effortful processing and high levels of cognitive resources (H. Christensen, 2001; Hedden & Gabrieli, 2004; D. C. Park & Reuter-Lorenz, 2009). When assessed at the same age, later born cohorts tend to outperform earlier born cohorts on cognitive tasks, a finding known as

the “Flynn effect” (Flynn, 1987). Growing evidence suggests that cohort improvements in cognitive performance are maintained across the life span (e.g., Bowles, Grimm, & McArdle, 2005; Pietschnig & Voracek, 2015; Rodgers, 1998; Rönnlund & Nilsson, 2009; Skirbekk, Stonawski, Bonsang, & Staudinger, 2013; Trahan, Stuebing, Fletcher, & Hiscock, 2014). In the global context of population aging and related health care concerns, the finding that cognitive performance may get better across generations

holds promise for extending the window of healthy and productive aging. A continuation of cohort improvements in cognitive functioning could offset the age-related cognitive decline. This would imply that, despite living longer, later born cohorts would not live in poorer cognitive health compared with earlier born cohorts. (Skirbekk et al., 2013).

Evidence on cohort differences in cognitive aging is mixed and depends on several factors such as the cognitive domains assessed, participants' age range, the number of years between birth cohorts, and whether studies examined cohort differences in levels or trajectories of cognitive performance. Previous studies that investigated birth cohort differences in level of cognitive performance in late life found better performance in a later born cohort (1926–1948), compared with an earlier born cohort (1900–1925) in memory, verbal, and spatial ability, but not in processing speed at age 67.5 (Finkel, Reynolds, McArdle, & Pedersen, 2007); better performance in the 1914–1948 cohort compared with the 1886–1913 cohort in spatial orientation, word fluency, inductive reasoning, and verbal meaning, but not in numeric ability at age 70 (Gerstorf, Ram, Hoppmann, Willis, & Schaie, 2011); better performance in the 1908–1940 cohort compared with the 1893–1923 cohort in reasoning, spatial orientation, list recall, and test recall, but not in vocabulary at age 74 (Zelinski & Kennison, 2007); better performance in the 1932–1946 cohort compared with the 1910–1924 cohort in list recall, visual recall, and visual learning at age 61–75 (Baxendale, 2010); better performance in logical reasoning and spatial ability in more recent cohorts born in 1901–1902, 1906–1907, and 1930 and measured at age 70 (Karlsson, Thorvaldsson, Skoog, Gudmundsson, & Johansson, 2015); better performance in processing speed, executive function, letter fluency, and category fluency in the 1932–1943 cohort compared with the 1922–1931, 1912–1921, 1902–1911 cohorts aged 65 and older (Dodge, Zhu, Lee, Chang, & Ganguli, 2014); better perceptual speed performance at mean age 75 in the 1925–1948 cohort compared with 1901–1922 cohort (Gerstorf et al., 2015); better performance on the Mini-Mental State Examination (MMSE) and on a composite of five aging-sensitive cognitive tests in the 1915 cohort assessed at age 95 compared with the 1905 cohort assessed at age 93 (Christensen et al., 2013).

Whereas the studies above have consistently reported better levels of cognitive performance in later born cohorts compared with earlier born cohorts, studies that assessed cohort differences in cognitive trajectories reported mixed findings. Finkel and colleagues (2007) found no differences in cognitive decline from age 62 to age 78 in verbal, spatial, memory, and processing speed abilities between the 1926–1948 cohort and the 1900–1925 cohort. Also, Dodge and colleagues (2014) found no differences in rates of change in psychomotor speed and category fluency between the 1932–1941 cohort and the 1922–1931 cohort or the 1912–1921 cohort, as well as no differences in letter fluency between the 1932–1941 cohort and the 1922–1931 cohort

aged 65 and older. These findings are in line with the preserved differentiation hypothesis which posits that cohort differences in levels of cognitive performance are similarly preserved across the life span, resulting in similar (i.e., parallel) rates of cognitive decline between cohorts (Salthouse, 2006). A number of studies found evidence for steeper cognitive decline in earlier born cohorts. Dodge and colleagues (2014) found steeper decline in psychomotor speed and category fluency in the 1902–1911 cohort compared with the 1932–1943 cohort, as well as steeper decline in letter fluency in the 1902–1911 and the 1912–1922 cohorts compared with the 1932–1943 cohort, and steeper decline in executive function in the 1922–1931, 1912–1922, and 1902–1911 cohorts compared with the 1932–1943 cohort aged 65 and older. Gerstorf and colleagues (2011) found steeper decline in spatial orientation, inductive reasoning, word fluency, numeric ability, and verbal meaning from age 50 to age 80 in the earlier born cohort (1886–1913) compared with the later born cohort (1914–1948). Also, Zelinski and Kennison (2007) found steeper decline in vocabulary from age 77 to age 86 in the earlier born cohort (1893–1923) compared with the later born cohort (1908–1940). On the contrary, other studies found that later born cohorts showed steeper cognitive decline. Compared with the 1901 cohort, the 1906 and the 1930 cohorts showed steeper decline in spatial ability, and the 1930 cohort showed steeper decline in reasoning ability between age 70 and age 79 (Karlsson et al., 2015). Also, compared with the 1893–1923 cohort, the 1908–1940 cohort showed steeper decline in text and list recall between age 77 and age 86 (Zelinski & Kennison, 2007). These later findings support the differential preservation hypothesis (Salthouse, 2006) which posits that cohort differences in initial levels of cognitive performance are differentially preserved across the life span, leading to different rates of cognitive decline between cohorts.

Given the increase in educational attainment in most countries (including the Netherlands) over the 20th century (Breen, Luijkx, Müller, & Pollak, 2010), and in view of findings suggesting that education increases cognitive reserve (Stern, 2006), education seems a primary candidate able to account for cohort differences in cognitive functioning in late life. Although several studies reported that higher education attainment is associated with better cognitive performance in old age (e.g., Glymour, Kawachi, Jencks, & Berkman, 2008; Schneeweis, Skirbekk, & Winter-Ebmer, 2014; van Hooren et al., 2007), there is little consistent evidence suggesting that aging-related cognitive decline may be moderated by education attainment (for a review, see Lenehan, Summers, Saunders, Summers, & Vickers, 2015). Existing evidence suggests that education does not account or only partially accounts for cohort differences in levels and trajectories of cognitive functioning in late life. Karlsson and colleagues (2015) found that education accounted for cohort differences in levels of performance and rates of decline in spatial ability, but not in reasoning ability. Other

studies found that educational attainment did not account for cohort differences in levels of performance and rates of decline in various cognitive abilities (Christensen et al., 2013; Dodge et al., 2014; Gerstorf et al., 2015; Gerstorf et al., 2011).

Our study aims to expand on previous findings by examining cohort differences in cognitive performance and rates of change in immediate recall, delayed recall, inductive reasoning, processing speed, and general cognitive performance. Furthermore, this study aims to examine whether education may account for any observed cohort differences in levels of performance and rates of change in these cognitive abilities.

Methods

Participants

Data were used from the Longitudinal Aging Study Amsterdam (Huisman et al., 2011), an ongoing study that focuses on understanding the interplay of physical, emotional, cognitive, and social functioning in late life. Respondents were recruited from three culturally distinct regions in the Netherlands. The first wave of data was collected in 1992–1993 among a sample of respondents aged 55–84 years. Since then measurement cycles were conducted in this sample about every 3 years. In 2002–2003, a first wave of data was collected for another sample of respondents aged 55–64 years. Since then respondents from this sample were also followed up about every 3 years.

The two birth cohorts included in the present study were selected based on an age range between 65 and 75 years at the moment of the baseline assessments. This age range was used to ensure that repeated measures of all cognitive abilities were available and that there was no overlap between birth cohorts across measurement waves. The first cohort included in the present study was born between 1920 and 1930, whereas the second cohort was born between 1931 and 1941. The cycle 1995–1996 was considered the baseline measurement for the first birth cohort ($N = 705$), whereas the cycle 2005–2006 was considered the baseline for the second birth cohort ($N = 646$). For the first cohort, follow-up measurements were conducted in 1998–1999 and 2001–2002. The second cohort was followed up in 2008–2009 and 2011–2012.

Instruments

General cognitive performance was assessed using the MMSE (Folstein, Folstein, & McHugh, 1975). The instrument is widely used in epidemiological studies to screen for cognitive impairment and to assess general cognitive function/mental status in older adults and shows satisfactory reliability and construct validity (Tombaugh & McIntyre, 1992). MMSE scores range from 0 to 30 with higher scores indicating better cognitive performance. In our study, we used the scale score based on the maximum

score of spelling or subtraction. Because the MMSE score is negatively skewed at all waves, it was transformed ($\ln[31 - \text{MMSE score}]$) to obtain a near-normal distribution.

Episodic memory was assessed using the 15 Words Test, a Dutch version of the Auditory Verbal Learning Test (Rey, 1964). The procedure started with a verbal presentation of 15 words, which were repeated during three trials, and participants had to report the words they remembered after each trial. The total score of the three trials was used as a measure of immediate recall, and the score could range between 0 and 45. After a distraction period of about 20 minutes, participants were asked to recall the words they had learned. This was used as a measure of delayed recall, and the total score could range between 0 and 15. To avoid learning effects, at the first follow-up participants in both cohorts were administered a different version of the test from the one used at baseline (i.e., they had to memorize a different list of words). At the second follow-up, they received again the same version of the memory test as the one used at baseline.

Information processing speed was assessed using the Coding Task, also known as the Digit-Symbol Substitution subtest of the Wechsler Adult Intelligence Scale (Wechsler, 1987). In the adapted form of the Coding Task used in Longitudinal Aging Study Amsterdam (LASA), participants were shown two rows of characters and have to match the characters from the upper row with characters from the lower row using as many combinations as possible. They were asked to name the corresponding character during three trials, each lasting for 1 minute. We used the total score for the three trials, which could range between 0 and 138. Because the original task was adapted to require a verbal rather than a motor response, it is considered that the test measures cognitive speed rather than motor speed processes.

Inductive reasoning was assessed using the Raven Colored Progressive Matrices (Raven, 1995). Participants were presented with a drawing from which a pattern was missing and they had to choose the correct missing pattern from six alternatives. Raven consists originally of three trials, but in LASA only the first and last trials were used. The test shows a progressive increase in difficulty and scale scores range from 0 to 24. Poor performance on this task is considered a good marker of dementia (Gainotti, Parlato, Monteleone, & Carlomagno, 1992).

Whereas for log-transformed MMSE, lower scores reflect better performance, for all other cognitive measures, a higher score reflects better performance. We used age, gender, education attainment, and number of chronic diseases as covariates. We chose to adjust for cohort differences in the number of chronic diseases based on previous findings of LASA showing that the prevalence of chronic diseases increases in the later born cohort (Deeg, van Vliet, Kardaun, & Huisman, 2013) and that chronic diseases predict decline in several domains of cognitive functioning (Comijs et al., 2009). Education attainment was measured

as the number of years of schooling. The number of chronic diseases was based on self-reports and included chronic nonspecific lung disease, cardiac disease, peripheral arterial disease, diabetes mellitus, cerebrovascular accident or stroke, osteoarthritis or rheumatoid arthritis, cancer, hypertension, and a maximum of two other diseases. Compared with general practitioner information, the accuracy of self-reports of these diseases was shown to be adequate (Kriegsman, Penninx, van Eijk, Boeke, & Deeg, 1996).

Statistical Analysis

Linear mixed model analyses were conducted in SPSS (version 22) to examine cohort differences in baseline performance and rates of change in several cognitive abilities. We used maximum likelihood (ML) estimation which calculates parameters using both cases with complete data and cases with partially missing data. The ML estimator deals with missing data under the missing at random (MAR) assumption. When the missing data mechanism is MAR, missing data is assumed to be “noninformative” or “ignorable,” and it can be predicted by variables included in the model (Little & Rubin, 1987). In this case, the estimation of the model parameters in the presence of missing data would be as if data had been complete. The inclusion of several covariates in our models (i.e., age, gender, chronic diseases, and education) helped to improve the accuracy of the estimates of cohort differences in cognitive functioning under the MAR assumption.

Inductive reasoning was only measured at baseline and at the first follow-up, whereas all other cognitive abilities were also measured at the second follow-up. For immediate recall, delayed recall, processing speed, and inductive reasoning, we used raw scores whereas for MMSE, we used log-transformed scores. A first set of models examined cohort differences in baseline cognitive performance adjusting for age, gender, and number of chronic diseases. A second set of models examined cohort differences in baseline cognitive performance adjusting not only for age, gender, and number of chronic diseases, but also for education (measured as years of schooling). A third set of models included an interaction term between time and cohort to examine cohort differences in cognitive change adjusting for age, gender, and number of chronic diseases. Finally, a fourth set of models reexamined cohort differences in cognitive change adjusting not only for age, gender, and number of chronic diseases, but also for education. Significant interaction effects were followed up by stratified analyses by cohort with the aim to examine whether each cohort experienced significant cognitive decline overtime. One set of stratified analyses adjusted only for age, gender, and chronic diseases, and another set of stratified analyses adjusted also for education. For each model, effect sizes were calculated by dividing each estimate by the standard deviation of the outcome.

Sensitivity analyses were conducted to examine whether attrition may bias findings of cohort differences in cognitive decline. We started by examining the missing data patterns in each cohort. Second, we compared the reasons for dropout between cohorts. Third, we conducted logistic regression analyses to examine the predictors of dropout (i.e., baseline cognitive performance, age, gender, education, and number of chronic diseases) in each cohort. Fourth, we examined cohort differences in cognitive decline only among study completers (those with observed data at all time points). Fifth, pattern mixture analyses were conducted to examine whether findings of cohort differences in cognitive decline may be affected by specific missing data patterns.

Results

Descriptive statistics are presented in Table 1, including the number of participants in each cohort who contributed data on each measure at each assessment occasion. Findings from linear mixed models are presented in Table 2. The first set of models examined cohort differences in baseline cognitive performance adjusted for age, gender, and number of chronic diseases, but unadjusted for education. Findings from these models suggest that the later born cohort had statistically significant higher levels of general cognitive performance, inductive reasoning, and processing speed at baseline, whereas no significant cohort differences were found for immediate and delayed recall.

A second set of models examined cohort differences in baseline cognitive performance adjusting not only for age, gender, and number of chronic diseases, but also for education. These models suggest that cohort differences in inductive reasoning and general cognitive performance were no longer significant after adjusting for education. However, later born participants continued to show significantly faster processing speed, and they also showed significantly lower levels of immediate recall compared with earlier born participants.

A third set of models examined cohort differences in cognitive change by including an interaction term between cohort and time in the context of adjustment for age, gender, and number of chronic diseases, but not education. The later born cohort showed steeper decline in processing speed overtime. The later born cohort also showed steeper decline in immediate and delayed recall but only between baseline and the first follow-up assessment (when a different word list was administered). Between baseline and the second follow-up assessment (when the same word list was administered), the later born cohort showed shallower decline in immediate and delayed recall compared with the earlier born cohort. We found no significant cohort differences in rates of change in general cognitive performance and inductive reasoning.

A fourth set of models examined cohort differences in cognitive change adjusting not only for age, gender, and number of chronic diseases, but also for education. Later

Table 1. Descriptive Statistics for Demographic Characteristics and Cognitive Abilities

Birth cohort 1 (1920–1930)	Baseline			Follow-up			Follow-up		
	1995–1996			1998–1999			2001–2002		
	(age 65–75 years)			(age 68–78 years)			(age 71–81 years)		
	<i>N</i>	Mean	<i>SD</i>	<i>N</i>	Mean	<i>SD</i>	<i>N</i>	Mean	<i>SD</i>
Age	705	69.8	2.8						
Education	704	9.0	3.2						
Chronic diseases	705	1.6	1.3						
Inductive reasoning	692	18.6	3.7	595	18.1	3.7			
Processing speed	685	76.9	20.2	594	75.9	18.9	487	74.2	19.8
Immediate recall	694	21.3	5.8	593	20.1	5.9	491	21.1	6.5
Delayed recall	694	6.7	2.8	590	6.1	2.9	490	6.5	3.2
General cognitive performance	705	27.6	2.2	618	27.5	2.4	525	27.2	2.6

Birth cohort 2 (1931–1941)	Baseline			Follow-up			Follow-up		
	2005–2006			2008–2009			2011–2012		
	(age 65–75 years)			(age 68–78 years)			(age 71–81 years)		
	<i>N</i>	Mean	<i>SD</i>	<i>N</i>	Mean	<i>SD</i>	<i>N</i>	Mean	<i>SD</i>
Age	646	69.5	3.0						
Education	646	10.0	3.4						
Chronic diseases	646	1.9	1.3						
Inductive reasoning	640	19.2	3.4	528	18.8	3.5			
Processing speed	635	81.5	19.5	525	79.3	20.1	431	77.1	19.3
Immediate recall	637	21.1	6.1	523	18.8	5.5	441	21.5	6.1
Delayed recall	635	6.6	2.9	523	5.5	2.7	439	6.6	3.0
General cognitive performance	646	27.9	2.2	554	27.8	2.2	477	27.7	2.4

Note: Age and education were measured in years; in the earlier born cohort, 52.3% of participants were women, whereas in the later born cohort 53.7% of participants were women; for inductive reasoning, data were only available at baseline and at the first follow-up.

born participants continued to show steeper decline in processing speed overtime. Also, later born participants continued to show steeper decline in immediate recall and delayed recall between Time 1 and Time 2, as well as shallower decline in delayed recall between Time 1 and Time 3. We found no significant cohort differences in rates of change in general cognitive performance and inductive reasoning. Significant interaction effects were followed up by stratified analyses by cohort. Because the significance, sign, and magnitude of the interaction effects were similar before and after adjusting for education, we only present stratified results for the fully adjusted models (Supplementary Table 1). Results from stratified analyses suggest that participants in each cohort showed significant decline in processing speed overtime. The earlier born cohort showed significant decline in immediate and delayed recall from Time 1 to Time 2, as well as from Time 1 to Time 3, whereas the later born cohort showed significant decline in immediate and delayed recall only from Time 1 to Time 2. Based on the fourth set of models, we present a figure illustrating the main findings of cohort differences

in cognitive functioning (Figure 1), as well as two tables presenting the effects of all covariates (i.e., time, cohort, age, gender, chronic diseases, and education) on cognitive outcomes (Supplementary Tables 2 and 3).

Additional analyses were conducted to examine the robustness of our findings to the effect of attrition. Two main patterns of missing data were identified. Pattern 1 included those who had missing data at both Time 2 and Time 3. Pattern 2 included those who had missing data only at time 3. More than 97% of cases consisted of study completers (i.e., those with observed data at all time points), those with missing data Pattern 1, and those with missing data Pattern 2. Less than 3% of participants had missing data corresponding to a different pattern (e.g., missing only at Time 2). The percentage of participants who completed the study and the percentage of those with specific missing data patterns were similar between cohorts (Supplementary Table 4). In both cohorts, the main reason for dropout was mortality; other reasons included refusal, ineligibility, and lack of contact (Supplementary Table 5). The following predictors of dropout were identified in both cohorts:

Table 2. Cohort Differences in Baseline Cognitive Performance and Rates of Change

	Models unadjusted for education				Models adjusted for education			
		95% CI				95% CI		
	<i>B</i>	Lower bound	Upper bound	Effect size	<i>B</i>	Lower bound	Upper bound	Effect size
Cohort differences in cognitive performance at baseline								
MMSE	0.09**	0.02	0.16	0.14	0.03	−0.04	0.09	0.04
Immediate recall	0.27	−0.35	0.89	0.04	0.79*	0.19	1.39	0.13
Delayed recall	0.12	−0.18	0.42	0.04	0.29	−0.01	0.59	0.10
Processing speed	−5.02***	−7.14	−2.90	0.25	−2.54*	−4.51	−0.57	0.13
Inductive reasoning	−0.57**	−0.95	−0.19	0.16	−0.16	−0.52	0.19	0.04
Cohort differences in cognitive change (time by cohort interactions)								
MMSE								
Time (1 vs. 2)	0.01	−0.06	0.08	0.01	0.01	−0.06	0.08	0.01
Time (1 vs. 3)	0.07	−0.01	0.15	0.11	0.07	−0.01	0.14	0.11
Immediate recall								
Time (1 vs. 2)	1.16***	0.55	1.77	0.19	1.17***	0.56	1.77	0.19
Time (1 vs. 3)	−0.65*	−1.30	<−0.01	0.11	−0.62	−1.27	0.02	0.10
Delayed recall								
Time (1 vs. 2)	0.41**	0.12	0.70	0.14	0.41**	0.12	0.70	0.14
Time (1 vs. 3)	−0.32*	−0.64	−0.01	0.11	−0.31*	−0.62	<−0.01	0.11
Processing speed								
Time (1 vs. 2)	1.47*	0.28	2.65	0.07	1.50*	0.32	2.69	0.08
Time (1 vs. 3)	2.71***	1.43	3.99	0.14	2.76***	1.48	4.04	0.14
Inductive reasoning								
Time (1 vs. 2)	−0.06	−0.41	0.30	0.02	−0.04	−0.40	0.31	0.01

Notes: CI = confidence interval; MMSE = Mini-Mental State Examination.

MMSE estimates are based on log-transformed scores obtained using the formula ($\ln[31 - \text{MMSE score}]$), with lower scores reflecting better general cognitive performance. For cohort, the reference category is the later born cohort. For gender, the reference category is female. All models are adjusted for age, gender, and number of chronic diseases at baseline. Effect sizes were calculated by dividing the estimate by the standard deviation of the outcome.

* $p < .05$. ** $p < .01$. *** $p < .001$.

being male, having a higher number of chronic diseases, and having lower baseline levels of immediate recall, processing speed and inductive reasoning. Older age at baseline and lower levels of delayed recall and general cognitive performance at baseline predicted dropout rates only in the earlier born cohort. Education attainment did not predict dropout rates in either cohort (Supplementary Table 5).

Linear mixed models that included only study completers (Supplementary Table 6) suggest that findings of cohort differences in cognitive decline were similar with findings from the initial analyses that included all participants (i.e., completers as well as dropout cases). The only different finding is that cohort differences in immediate recall from Time 1 to Time 3 failed to reach statistical significance when only study completers were included in the analysis (the effect was marginally significant). Pattern mixture analyses were also conducted to examine whether cohort differences in cognitive decline may vary as a function of the missing data patterns. For the missing data Pattern 1, we calculated cohort by dropout interactions, but it was not possible to examine time by dropout interactions because data were observed only at Time 1. For the missing data Pattern 2 (including observed data at Time 1 and Time 2), we calculated time by cohort by dropout interactions,

as well as time by dropout, and cohort by dropout interactions. Time by cohort by dropout (Pattern 2) interactions were not statistically significant, suggesting that changes in cognitive performance overtime in persons with missing data compared with those without missing were similar between cohorts. The only significant interaction between time and dropout (Pattern 2) was found for processing speed ($B = 2.51$, $p < .05$), suggesting that participants who dropped out at Time 3 showed steeper cognitive decline from Time 1 to Time 2 compared with participants who did not dropout at Time 3, regardless of cohort. Cohort by dropout interactions (Pattern 1 and Pattern 2) were not statistically significant, suggesting that cohorts had similar missing data patterns. Adjusting for dropout (Pattern 1 or Pattern 2) did not change findings of cohort differences in cognitive decline (Supplementary Table 7).

Discussion

Using data from LASA, the present study builds on previous findings of cohort differences in baseline performance and rates of change in various cognitive abilities. In the absence of adjustment for education, the later born cohort showed better general cognitive performance, inductive reasoning,

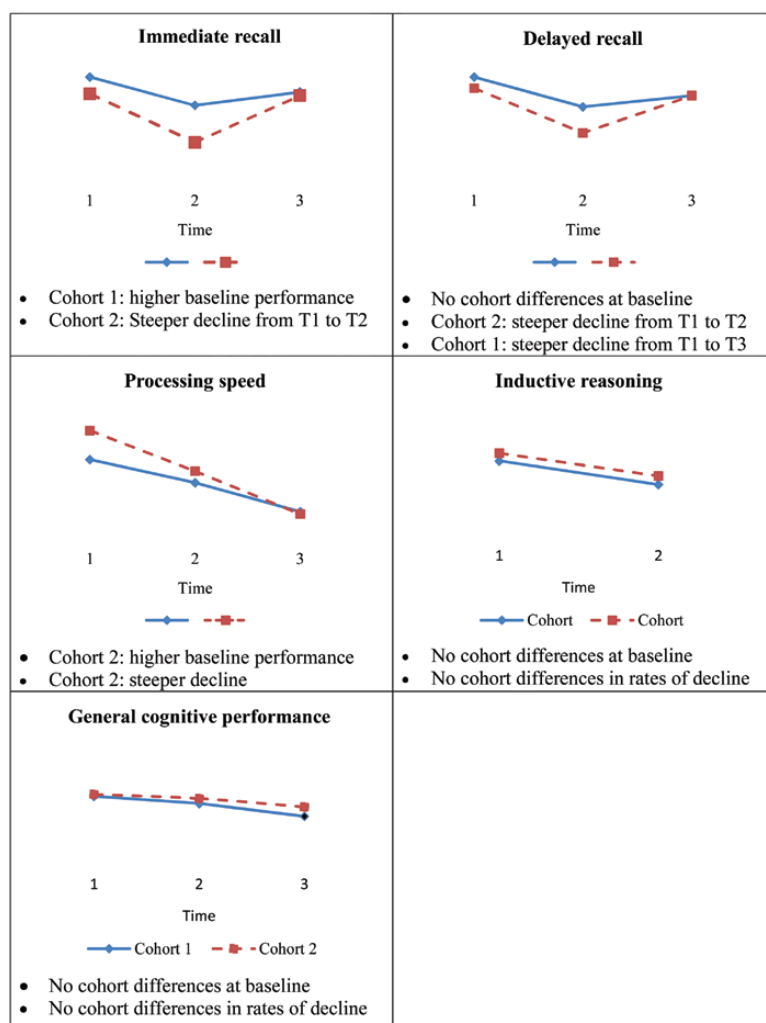


Figure 1. Cohort differences in baseline cognitive performance and rates of decline. Cohort 1 = earlier born cohort; Cohort 2 = later born cohort; for inductive reasoning, data were available only at Time 1 and Time 2; results presented in this figure are based on the fully adjusted models (i.e., controlling for age, gender, chronic diseases, and education).

and processing speed, whereas no cohort differences in immediate and delayed recall were found at baseline. After adjustment for education, cohort differences in baseline levels of general cognitive performance and inductive reasoning were no longer found, whereas the later born cohort continued to show faster processing speed. We found no significant cohort differences in rates of change in general cognitive performance and inductive reasoning. However, the later born cohort showed steeper decline in processing speed. The later born cohort also showed steeper decline in immediate and delayed recall but only between baseline and the first follow-up assessment when a different word list was administered. In contrast, the later born cohort showed shallower decline in immediate and delayed recall between baseline and the second follow-up assessment when the same word list was administered. Cohort differences in immediate recall decline between baseline and the second follow-up were no longer found after adjusting for education. Education did not account for cohort differences in cognitive change in any of the other cognitive abilities measured.

The finding that the later born cohort showed better general cognitive performance, processing speed, and inductive reasoning at baseline is consistent with the observation of an increase in cognitive test scores across generations, also known as the “Flynn effect” (Flynn, 1987). The finding that education accounted for cohort differences in general cognitive performance and inductive reasoning is consistent with predictions of the cognitive reserve theory (e.g., Stern, 2002; Stern, 2009). Our finding that education did not account for cohort differences in processing speed is consistent with that of Dodge and colleagues (2014) showing that the 1932–1943 birth cohort had faster processing speed than the 1922–1931 birth cohort aged 65 and older and that the effect persisted after adjustment for education. An unexpected finding is that cohorts showed no differences in memory performance at baseline before adjusting for education, but the earlier born cohort had better immediate recall performance after adjusting for education. This may suggest that older adults in the later born cohort draw upon their higher education to achieve good performance on memory tasks. When adjusting for

differences in education attainment between cohorts, the later born cohort no longer benefits from the facilitating effect of education and shows poorer memory performance than the earlier born cohort. The superior memory performance in the earlier born cohort may suggest a shift from rote learning in earlier born cohorts to more meaningful and active learning in later born cohorts (Schaie, 2008), or it may suggest that the memory test administered contains words that are more familiar to earlier born cohorts.

The finding that cohorts showed similar rates of change in general cognitive performance and inductive reasoning provides support for the preserved differentiation hypothesis whereby cohort differences in cognitive performance are similarly preserved overtime, leading to parallel rates of decline in the two cohorts (Salthouse, 2006). However, in line with the differential preservation hypothesis, we found that cohorts showed different rates of decline in processing speed and memory. Steeper decline in processing speed was found in the later born cohort both before and after adjusting for education. These findings are at odds with those of Dodge and colleagues (2014) who found no significant differences in processing speed decline between the 1922–1931 cohort and the 1932–1943 cohort either before or after adjusting for education. Several factors could explain the discrepancy between these findings. First, the study by Dodge and colleagues (2014) included participants who were aged 65 and older at study entry and there was no upper age limit, whereas our study included participants who were aged 65 to 75 years at study entry. Second, whereas the study by Dodge and colleagues (2014) included a task that measured psychomotor speed (i.e., Trail Making Test), our study included an adapted version of the Coding Task which requires a verbal rather than a motor response, thus assessing cognitive speed rather than motor speed processes. Third, the study by Dodge and colleagues (2014) eliminated participants with cognitive impairment (i.e., a score of 21 or below on the MMSE), whereas our study did not select participants based on their level of cognitive functioning.

In interpreting findings of cohort differences in memory decline, it is of note that the same word list was administered to both cohorts at Time 1 and Time 3 and a different word list was administered to both cohorts at Time 2. In both cohorts, we found that decline from Time 1 to Time 2 was steeper than decline from Time 1 to Time 3. This may be due to the greater difficulty of the memory test administered at Time 2, or it may indicate a learning effect between Time 1 and Time 3 when the same memory test was administered. We found that the later born cohort showed steeper decline from Time 1 to Time 2, but shallower decline from Time 1 to Time 3, compared with the earlier born cohort. The steeper decline from Time 1 to Time 2 in the later born cohort may suggest that words presented at Time 2 were less familiar to later born participants, which led to poorer performance in this cohort. It was previously suggested that a drop in the mean difference in education levels between cohorts over assessment waves may cause steeper memory

decline in later born participants who lose the advantage of higher education on cognitive function (Zelinski & Kennison, 2007). However, this was not the case in our study. The shallower decline from Time 1 to Time 3 in the later born cohort may suggest that later born participants have better cognitive reserve. Alternatively, this finding may suggest that the later born cohort experiences stronger learning effects between Time 1 and Time 3. However, we believe this is unlikely given the relatively long interval between the first and the third assessment.

We found that education accounted for cohort differences in initial levels of performance in some cognitive domains. These findings may suggest that higher education attainment in later born cohorts may have increased their cognitive reserve, allowing them to tolerate more aging-related neuropathology and maintain better cognitive performance than earlier born cohorts. However, our findings indicate that the later born cohort did not show a superior preservation of cognitive abilities overtime compared with the earlier born cohort, either before or after adjusting for education. These findings may suggest that, once a certain threshold on neuropathological burden is reached and brain reserve/cognitive reserve is exhausted, later born cohorts may experience steeper cognitive decline than earlier born cohorts. In support of these hypothesis, previous studies suggest that cognitive reserve may no longer facilitate cognitive performance once dementia-related neuropathology sets in (Amieva et al., 2014; Hall et al., 2007; Stern, Albert, Tang, & Tsai, 1999). This may explain previous findings suggesting that, despite higher educational attainment, later born cohorts experience steeper terminal cognitive decline (i.e., an acceleration of the rate of cognitive decline before death) compared with earlier born cohorts (Gerstorf et al., 2015; Hülür, Infurna, Ram, & Gerstorf, 2013). Although our study did not directly examine mortality- or dementia-related cognitive decline, our findings suggest that cognitive reserve cannot offset the aging-related brain changes that underlie cognitive decline in community-dwelling older adults. In interpreting current findings, it is of note that our later born cohort had only 1 year of education more than the earlier born cohort. A stronger effect of education on cohort differences in levels and trajectories of cognitive functioning may be observed with larger increases in educational attainment across cohorts. Alternatively, cohort differences in cognitive decline may be better accounted for by factors such as occupational attainment or leisure activities that also contribute to increasing cognitive reserve and delaying cognitive impairment in later life (Scarmeas, Levy, Tang, Manly, & Stern, 2001; Stern, 2012; Stern et al., 1994; Valenzuela & Sachdev, 2006).

A potential limitation of our study is that our findings pertain only to cohorts aged 65 to 75 years at baseline, born 10 years apart, and followed up over 6 years. Future studies should clarify whether our findings can be replicated when longer follow-ups and longer time intervals between birth cohorts are used. Moreover, it remains to examine whether our findings on cohort differences in cognitive abilities in the younger old participants can be replicated in older old persons

and whether the protective effect of education on cognitive aging carries on in the last years of life. A common concern in longitudinal studies of aging is the selective dropout of persons with poor physical and cognitive health, which could affect the generalizability of findings. Although we found that persons with poorer baseline cognitive functioning and those with a higher number of chronic diseases were more likely to drop out from the study, the missing data patterns, the reasons for dropout and the predictors of dropout were similar between cohorts. Moreover, complete case analyses and pattern mixture analyses revealed that attrition did not significantly impact on findings of cohort differences in cognitive decline.

To conclude, our findings add to the growing evidence of cohort differences in levels of cognitive performance favoring later born cohorts and suggest that this effect may be partly due to cohort improvements in educational attainment. Our findings suggest that educational attainment may offer later born participants an initial edge in cognitive performance, but it does not slow down their cognitive decline. Understanding the extent to which cohort improvements in cognitive functioning could offset the effect of aging-related cognitive decline has implications for extending the phase of healthy aging and for adapting the workforce and health-care systems to meet the needs of aging societies.

Supplementary Material

Please visit the article online at <http://psychsocgerontology.oxfordjournals.org/> to view supplementary material.

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Conflict of Interest

None.

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3.1 SUPPLEMENTARY MATERIALS CHAPTER 3

These supplementary materials were presented in the following journal publication:

Brailean, A., Huisman, M., Prince, M., Prina, A. M., Deeg, D. J. H., & Comijs, H. (2016). Cohort Differences in Cognitive Aging in the Longitudinal Aging Study Amsterdam. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences.*, Advance online publication. doi:10.1093/geronb/gbw129

Supplementary Table 1. Changes overtime in immediate recall, delayed recall and processing speed by cohort

	Mean score				95% CI		
	Time 1	Time 2	Time 3	B	Lower bound	Upper bound	Effect size
Earlier born cohort							
Immediate recall							
Time (1 vs. 2)	21.30	19.81		-1.48***	-1.90	-1.07	0.25
Time (1 vs. 3)	21.30		20.52	-0.78**	-1.22	-0.33	0.13
Delayed recall							
Time (1 vs. 2)	6.70	5.90		-0.80***	-1.00	-0.60	0.27
Time (1 vs. 3)	6.70		6.20	-0.51***	-0.72	-0.29	0.17
Processing speed							
Time (1 vs. 2)	76.78	74.71		-2.07***	-2.88	-1.25	0.11
Time (1 vs. 3)	76.78		72.28	-4.49***	-5.37	-3.62	0.23
Later born cohort							
Immediate recall							
Time (1 vs. 2)	21.10	18.43		-2.64***	-3.08	-2.19	0.44
Time (1 vs. 3)	21.10		20.94	-0.13	-0.61	0.34	0.02
Delayed recall							
Time (1 vs. 2)	6.57	5.36		-1.21***	-1.42	-0.99	0.42
Time (1 vs. 3)	6.57		6.39	-0.19	-0.41	0.04	0.07
Processing speed							
Time (1 vs. 2)	81.71	78.15		-3.56***	-4.43	-2.69	0.14
Time (1 vs. 3)	81.71		74.47	-7.24***	-8.17	-6.30	0.37

Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; all models are adjusted for age, gender, number of chronic diseases and education. Results stratified by cohort are presented only for linear mixed models in which time by cohort interaction effects were statistically significant.

Supplementary Table 2. Effects of cohort, gender, age, chronic diseases, education and time, on general cognitive performance, processing speed and inductive reasoning

Model	Unadjusted for education			Adjusted for education		
	B	95% C.I.		B	95% C.I.	
		Lower Bound	Upper Bound		Lower Bound	Upper Bound
General cognitive performance						
<i>Intercept</i>	-0.63	-1.31	0.05	0.21	-0.43	0.85
<i>Main effects</i>						
Cohort	0.09**	0.02	0.16	0.03	-0.04	0.09
Gender	0.03	-0.02	0.09	0.12***	0.07	0.17
Age	0.02***	0.01	0.03	0.02***	0.01	0.03
Chronic diseases	0.03**	0.01	0.05	0.02*	<0.00	0.04
Education				-0.06***	-0.07	-0.05
Time 1 vs. 3	0.06*	<0.01	0.11	0.06*	0.01	0.12
Time 1 vs. 2	0.03	-0.02	0.09	0.04	-0.01	0.09
Processing speed						
<i>Intercept</i>	156.11***	131.15	181.08	121.40***	98.36	144.45
<i>Main effects</i>						
Cohort	-5.01***	-7.15	-2.87	-2.52*	-4.50	-0.54
Gender	-2.81**	-4.87	-0.76	-6.47***	-8.39	-4.56
Age	-1.00***	-1.36	-0.64	-0.85***	-1.18	-0.52
Chronic diseases	-1.90***	-2.70	-1.10	-1.39***	-2.13	-0.66
Education				2.49***	2.20	2.78
Time 1 vs. 3	-7.20***	-8.13	-6.27	-7.25***	-8.18	-6.32
Time 1 vs. 2	-3.54***	-4.40	-2.67	-3.57***	-4.43	-2.70
Inductive reasoning						
<i>Intercept</i>	26.62***	22.36	30.87	20.99***	17.03	24.96
<i>Main effects</i>						
Cohort	-0.56**	-0.94	-0.18	-0.17	-0.53	0.19
Gender	0.67***	0.32	1.02	0.07	-0.26	0.40
Age	-0.11**	-0.17	-0.04	-0.08**	-0.14	-0.02
Chronic diseases	-0.24**	-0.37	-0.10	-0.15*	-0.28	-0.03
Education				0.41***	0.36	0.46
Time 1 vs. 2	-0.55***	-0.81	-0.30	-0.56***	-0.82	-0.30

Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; MMSE estimates are based on log-transformed scores obtained using the formula ($\ln[31 - \text{MMSE score}]$). Lower log transformed MMSE scores reflect better cognitive performance. For cohort the reference category is the later born cohort. For gender the reference category is female.

Supplementary Table 3. Effects of cohort, time, gender, age, chronic diseases and education on immediate and delayed recall

Model	Unadjusted for education			Adjusted for education		
	B	95% C.I.		B	95% C.I.	
		Lower Bound	Upper Bound		Lower Bound	Upper Bound
Immediate recall						
<i>Intercept</i>	44.75***	38.11	51.40	37.83***	31.43	44.23
<i>Main effects</i>						
Cohort	0.29	-0.34	0.91	0.79*	0.19	1.40
Gender	-2.68***	-3.23	-2.13	-3.40***	-3.93	-2.86
Age	-0.32***	-0.41	-0.22	-0.29***	-0.38	-0.19
Chronic diseases	-0.24*	-0.45	-0.03	-0.14	-0.34	0.07
Education				0.49***	0.41	0.57
Time 1 vs. 3	-0.11	-0.58	0.36	-0.14	-0.61	0.32
Time 1 vs. 2	-2.63***	-3.07	-2.19	-2.64***	-3.08	-2.20
Delayed recall						
<i>Intercept</i>	15.51***	12.27	18.74	13.00***	9.81	16.19
<i>Main effects</i>						
Cohort	0.15	-0.15	0.45	0.33*	0.03	0.63
Gender	-1.42***	-1.68	-1.15	-1.68***	-1.94	-1.41
Age	-0.12***	-0.16	-0.07	-0.10***	-0.15	-0.06
Chronic diseases	-0.12*	-0.23	-0.02	-0.09	-0.19	0.01
Education				0.18***	0.14	0.22
Time 1 vs. 3	-0.18	-0.40	0.05	-0.19	-0.42	0.04
Time 1 vs. 2	-1.21***	-1.42	-1.00	-1.21***	-1.42	-1.00

Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; for cohort the reference category is the later born cohort; for gender the reference category is female.

Supplementary Table 4. Missing data patterns by cohort

Cognitive measure	Completers	Pattern 1	Pattern 2	Other patterns
Cohort 1 (N = 705)				
Immediate recall	68%	14%	16%	2%
Delayed recall	68%	14%	15%	3%
Processing speed	67%	14%	16%	3%
MMSE	74%	12%	14%	0%
Inductive reasoning	84%	14%	N/A	2%
Cohort 2 (N = 646)				
Immediate recall	64%	14%	16%	3%
Delayed recall	63%	14%	17%	3%
Processing speed	63%	15%	18%	2%
MMSE	72%	12%	14%	2%
Inductive reasoning	81%	18%	N/A	1%

Note: Completers are participants with observed data at all time points; pattern 1 consists of observed data at time 1 and missing data at time 2 and time 3; pattern 2 consists of observed data at time 1 and 2 and missing data at time 3.

Supplementary Table 5. Predictors of dropout and reasons for dropout by cohort

	Earlier born cohort			Later born cohort		
	O.R.	95% C.I.		O.R.	95% C.I.	
		Lower bound	Upper bound		Lower bound	Upper bound
Predictors of dropout						
Age	1.11**	1.03	1.18	1.03	0.96	1.10
Gender	0.46***	0.31	0.68	0.60*	0.40	0.89
No. chronic diseases	1.24**	1.07	1.42	1.25**	1.08	1.44
Education	1.01	0.94	1.06	0.94	0.88	1.00
Immediate recall	0.92***	0.89	0.95	0.95**	0.92	0.98
Delayed recall	0.89**	0.83	0.95	0.93	0.87	1.00
Processing speed	0.98**	0.97	0.99	0.98*	0.97	0.99
Inductive reasoning	0.93*	0.89	0.98	0.92*	0.87	0.98
MMSE	0.92*	0.85	0.99	0.94	0.86	1.02
Reasons for dropout						
Mortality	80%			57%		
Refusal	12%			28%		
Ineligibility	7%			14%		
Not contacted	1%			1%		

Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; all predictors were assessed at baseline; for gender the reference category is female.

Supplementary Table 6. Cohort differences in cognitive change among study completers

Model	Unadjusted for education			Adjusted for education		
	B	95% CI		B	95% CI	
		Lower bound	Upper bound		Lower bound	Upper bound
Time by cohort interactions						
MMSE						
Time (1 vs. 2)	<-0.01	-0.08	0.07	<-0.01	-0.08	0.08
Time (1 vs. 3)	0.06	-0.02	0.14	0.06	-0.02	0.14
Immediate recall						
Time (1 vs. 2)	1.23***	0.54	1.92	1.23***	0.54	1.92
Time (1 vs. 3)	-0.62	-1.31	0.06	-0.62	-1.31	0.06
Delayed recall						
Time (1 vs. 2)	0.44**	0.11	0.78	0.44**	0.11	0.78
Time (1 vs. 3)	-0.35*	-0.69	-0.01	-0.35*	-0.69	-0.01
Processing speed						
Time (1 vs. 2)	1.50*	0.18	2.82	1.49*	0.17	2.81
Time (1 vs. 3)	2.91***	1.59	4.23	2.90***	1.58	4.22
Inductive reasoning						
Time (1 vs. 2)	-0.04	-0.40	0.32	-0.04	-0.40	0.31

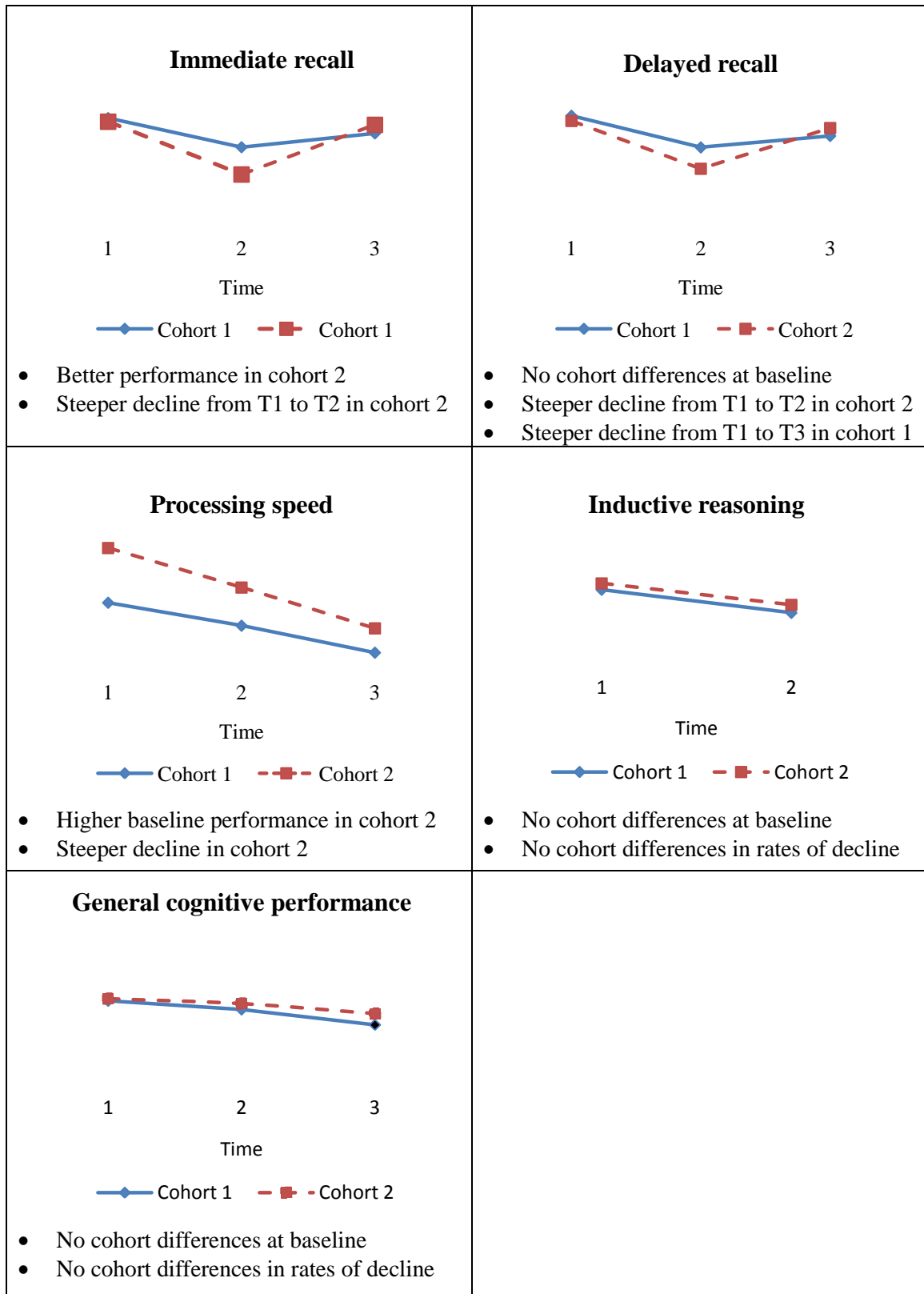
Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; all models were adjusted for age, gender and number of chronic diseases.

Supplementary Table 7. Cohort differences in cognitive change adjusting for dropout patterns

Model	Unadjusted for education			Adjusted for education		
	B	95% CI		B	95% CI	
		Lower bound	Upper bound		Lower bound	Upper bound
Time by cohort interactions						
Pattern 1						
MMSE						
Time (1 vs. 2)	0.01	-0.06	0.08	0.01	-0.06	0.08
Time (1 vs. 3)	0.07	-0.01	0.15	0.07	-0.01	0.14
Immediate recall						
Time (1 vs. 2)	1.15***	0.54	1.76	1.16***	0.55	1.76
Time (1 vs. 3)	-0.65*	-1.30	<-0.01	-0.62	-1.27	0.02
Delayed recall						
Time (1 vs. 2)	0.41**	0.11	0.70	0.41**	0.12	0.70
Time (1 vs. 3)	-0.32*	-0.63	-0.01	-0.31*	-0.62	<-0.01
Processing speed						
Time (1 vs. 2)	1.39*	0.21	2.58	1.43*	0.25	2.61
Time (1 vs. 3)	2.69***	1.41	3.96	2.74***	1.46	4.01
Inductive reasoning						
Time (1 vs. 2)	-0.04	-0.39	0.31	-0.03	-0.38	0.32
Pattern 2						
MMSE						
Time (1 vs. 2)	0.01	-0.06	0.08	0.01	-0.07	0.08
Time (1 vs. 3)	0.07	-0.01	0.14	0.07	-0.01	0.14
Immediate recall						
Time (1 vs. 2)	1.16***	0.55	1.77	1.17***	0.56	1.77
Time (1 vs. 3)	-0.65*	-1.29	<-0.01	-0.62	-1.26	0.03
Delayed recall						
Time (1 vs. 2)	0.41**	0.12	0.70	0.41**	0.12	0.70
Time (1 vs. 3)	-0.32*	-0.63	-0.01	-0.31*	-0.62	<-0.01
Processing speed						
Time (1 vs. 2)	1.47*	0.28	2.66	1.51*	0.32	2.69
Time (1 vs. 3)	2.71***	1.43	4.00	2.77***	1.49	4.05

Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; pattern 1 consists of observed data at time 1 and missing data at time 2 and time 3; pattern 2 consists of observed data at time 1 and time 2 and missing data at time 3; all models were adjusted for age, gender and number of chronic diseases.

Supplementary Figure 1. Cohort differences in cognitive functioning

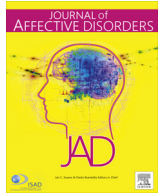


Note: cohort 1 = earlier born cohort; cohort 2 = later born cohort; for inductive reasoning data were available only at time 1 and time 2. Results presented in this figure are based on the fully adjusted models (i.e., controlling for age, gender, chronic diseases and education).

**CHAPTER 4: LATE-LIFE DEPRESSION SYMPTOM DIMENSIONS AND
COGNITIVE FUNCTIONING IN THE LONGITUDINAL AGING STUDY
AMSTERDAM (LASA)**

This chapter is presented as a published paper and it is the exact copy of the following journal publication:

Brailean, A., Comijs, H. C., Aartsen, M. J., Prince, M., Prina, A. M., Beekman, A., & Huisman, M. (2016). Late-life depression symptom dimensions and cognitive functioning in the Longitudinal Aging Study Amsterdam (LASA). *J Affect Disord*, 201, 171-178. doi:10.1016/j.jad.2016.05.027



Late-life depression symptom dimensions and cognitive functioning in the Longitudinal Aging Study Amsterdam (LASA)



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ABSTRACT

Background: Depression often co-occurs in late-life in the context of declining cognitive functions, but it is not clear whether specific depression symptom dimensions are differentially associated with cognitive abilities.

Methods: The study sample comprised 3107 community-dwelling older adults from the Longitudinal Aging Study Amsterdam (LASA). We applied a Multiple Indicators Multiple Causes (MIMIC) model to examine the association between cognitive abilities and latent dimensions of the Center for Epidemiologic Studies Depression Scale (CES-D), while accounting for differential item functioning (DIF) due to age, gender and cognitive function levels.

Results: A factor structure consisting of somatic symptoms, positive affect, depressed affect, and interpersonal difficulties fitted the data well. Higher levels of inductive reasoning were significantly associated with lower levels of depressed affect and somatic symptoms, whereas faster processing speed was significantly associated with lower levels of somatic symptoms. DIF due to age and gender was found, but the magnitude of the effects was small and did not alter substantive conclusions.

Limitations: Due to the cross-sectional context of this investigation, the direction of influence between depression symptom levels and cognitive function levels cannot be established. Furthermore, findings are relevant to non-clinical populations, and they do not clarify whether certain DIF effects may be found only at high or low levels of depression.

Conclusions: Our findings suggest differential associations between late-life depression dimensions and cognitive abilities in old age, and point towards potential etiological mechanisms that may underlie these associations. These findings carry implications for the prognosis of cognitive outcomes in depressed older adults.

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Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; CFA, Confirmatory Factor Analysis; CFI, Comparative Fit Index; DIF, Differential Item Functioning; DSM, Diagnostic and Statistical Manual of Mental Disorders; GDS, Geriatric Depression Scale; LASA, Longitudinal Aging Study Amsterdam; MDD, Major Depressive Disorder; MIMIC, Multiple Indicators Multiple Causes; RCPM, Raven Colored Progressive Matrices; RMSEA, Root Mean Square Error of Approximation; TLI, Tucker Lewis Index; WLSMV, Weighted Least Squares Mean and Variance-Adjusted

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1. Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, depression is a multi-dimensional construct consisting of depressed affect (i.e., dysphoria), low positive affect (i.e., anhedonia), and somatic symptoms (American Psychiatric Association, 2000). Compared to their younger counterparts, older adults have a lower prevalence of Major Depressive Disorder (Kessler et al., 2010), but a higher prevalence of subsyndromal depression (Meeks et al., 2011). Also, older adults express lower levels of depressed affect (e.g., feeling

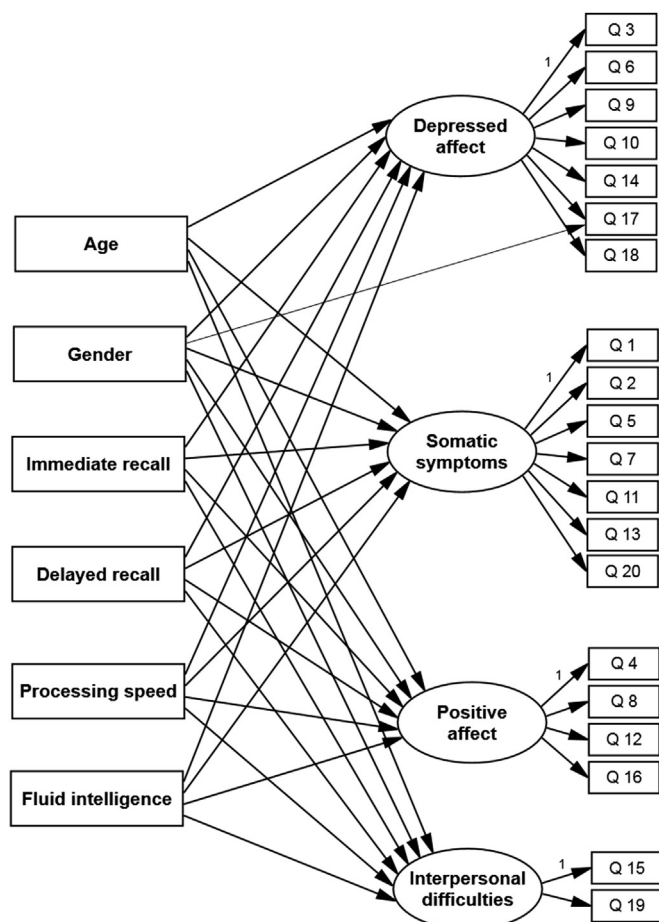


Fig. 1. MIMIC model showing the impact of age, gender and cognitive abilities on the CES-D measurement model with four factors. Due to space constraints, residual variances are not presented in the figure. Also, only one example of direct effect is illustrated, indicating gender differences in the probability of endorsing the CES-D item 17 (crying spells).

sad), but more pronounced somatic symptoms (e.g., fatigue, sleep disturbance, loss of appetite) and motivational symptoms (e.g., lack of interest or enjoyment) (Gallo et al., 1997; Hegeman et al., 2012a, 2012b). Studies conducted in older adults suggest a differential association between specific late-life depression dimensions (e.g., depressed affect, positive affect, somatic and motivational symptoms) and various health outcomes, such as brain function (Kirtan et al., 2014), functional disability and distress (Gallo et al., 1997), mortality (Blazer and Hybels, 2004; Gallo et al., 1997; John and Montgomery, 2009), cognitive impairment and decline (e.g., Baune et al., 2007; Castro-Costa et al., 2007; Turner et al., 2015), and incident dementia (Lugtenburg et al., 2016). A dimensional approach of depression could help clarify how different symptom presentations relate to various aging-related health outcomes and what etiological mechanisms may underlie these associations.

Although extensive evidence suggests that late-life depression co-occurs with impairment and decline in cognitive abilities such as memory, executive function, processing speed, and visuo-spatial abilities (e.g., Baudic et al., 2004; Comijs et al., 2001; Lockwood et al., 2002; Sheline et al., 2006), it is not clear whether the nature and severity of cognitive impairment differs among persons with specific symptom presentations. Existing reports suggest that motivational and somatic symptoms may be more strongly associated with vascular and degenerative processes (Naarding et al., 2005), as well as with cognitive impairment and Alzheimer Disease (Bartolini et al., 2005; Berger et al., 1999; Gallo et al., 1997; Kumar et al., 2006; Potvin et al., 2010), compared to mood

symptoms. Ageing-related dysfunctions in fronto-striatal structures and cerebrovascular disease have been postulated as possible mechanisms underlying the co-occurrence of executive dysfunction and motivational symptoms of depression (Alexopoulos, 2001). Instead, dysphoric symptoms may manifest as a psychological reaction to perceived cognitive decline in the early stages of impairment when older adults are aware of their cognitive dysfunctions. Low positive affect could also affect cognitive functioning by influencing dopamine levels (Ashby et al., 1999), cardiovascular risk (Davidson et al., 2010), and the attention scope (Fredrickson, 2001). The pattern of associations between specific depression dimensions and cognitive functioning and the neurobiological and psychological mechanisms that may underlie these associations are poorly understood. This is partly due to the scarcity of studies that employed a dimensional approach to depression, and partly due to methodological differences such as the assessment of depression symptom dimensions based on factor analytic studies of different depression scales, and the inclusion of clinically depressed patients or community-dwelling older adults.

Cross-sectional studies conducted in non-clinical populations using the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) suggest that: lower levels of depressed affect and somatic symptoms were related to better performance on tasks assessing speed, attention and executive function, whereas higher levels of positive affect were related to poorer verbal fluency performance (Baune et al., 2007); higher levels of positive affect (but not lower levels of depressed affect, somatic symptoms or interpersonal difficulties) were related to better everyday problem solving (Paterson et al., 2015); positive affect was the most robust predictor of cognitive performance across a variety of tasks assessing memory, processing speed, verbal fluency, visual retention, temporal orientation, and global cognition (La Rue et al., 1995). Studies using the Euro-D depression scale (Prince et al., 1999) found that verbal fluency performance was more strongly associated with motivational symptoms of depression than with affective suffering symptoms (Brailean et al.; Castro-Costa et al., 2007). Cross-sectional studies conducted in persons with MDD suggest that greater levels of apathy on the Hamilton Psychiatric Rating Scale for Depression (Williams, 1988) were associated with lower executive function and processing speed performance (Feil et al., 2003); greater levels of motivational symptoms on the Inventory of Depressive Symptomatology (Rush et al., 1996) were associated with poorer episodic memory and processing speed, whereas greater levels of mood symptoms were associated with poorer working memory and processing speed (Korten et al., 2014). A longitudinal study by Turner et al. (2015) suggests that lower levels of positive affect on the CES-D scale predicted decline in global cognition, episodic memory, and perceptual speed, whereas higher levels of anhedonic symptoms on the Geriatric Depression Scale (GDS) (Yesavage et al., 1982) predicted steeper decline in episodic memory, and higher levels of negative affect on the GDS predicted steeper decline in global cognition, as well as in episodic, semantic, and working memory.

Cognitive function levels may influence not only the severity of depressive symptoms, but also the type of symptoms reported. Given similar levels of depression severity, persons with poor cognitive functioning may be more likely to endorse certain items (e.g., concentration difficulties) than persons with normal cognitive functioning. Previous studies suggest that cognitive status may be related to response bias to several items assessing depression (Fieo et al., 2015; Mast, 2005). If items from depression scales measure different constructs in persons with low versus high cognitive functioning, measurement bias can impact on conclusions about the association between late-life depression and cognitive ageing; hence, the influence of measurement bias should be accounted for. In light of previous findings, it is also important

to account for differences in response behavior due to age and gender. For instance, there is evidence that older persons tend to under-report dysphoria and sadness (Gallo et al., 1994, 1999), and to over-report sleep difficulties, hopelessness, loss of interest, and slowing down (Christensen et al., 1999), whereas women are more likely than men to report having crying spells (Carleton et al., 2013; Yang and Jones, 2007; Yang et al., 2009), and less likely to report feeling like a failure (Yang et al., 2009).

The main aim of this study is to examine whether CES-D depression symptom dimensions (i.e., depressed affect, positive affect, somatic symptoms, and interpersonal difficulties) are differentially associated with performance in specific cognitive domains which are typically altered in late life depression (i.e., inductive reasoning, processing speed, immediate recall and delayed recall). A related aim is to examine item response biases due to age, gender and levels of cognitive functioning, and the extent to which item response biases affect the association between depression symptom dimensions and cognitive abilities.

2. Methods

2.1. Participants

Data were used from the Longitudinal Ageing Study Amsterdam (LASA) (Huisman et al., 2011), an ongoing study exploring physical, emotional, cognitive and social functioning in late life. Respondents were recruited from the population registers of 11 municipalities from three regions in the Netherlands and were interviewed in their homes by trained persons. The LASA study was approved by the Ethical Review Board of the VU University Medical Center and all respondents provided informed consent. The current study used data collected in 1992–1993 (LASA cycle wave B) from respondents aged 55–85 years old ($N=3107$). This data cycle (i.e., baseline assessment for the first LASA cohort) was selected because it included a larger sample size and a smaller amount of missing data.

2.2. Instruments

Depressive symptoms were measured using the CES-D (Radloff, 1977). Symptoms are assessed over the course of the past week and ratings to each item are based on a four-point scale 0–3). The total score of the 20 items ranges from 0 to 60, higher scores indicating more depressive symptoms. CES-D has good psychometric properties in older adults (Hertzog et al., 1990; Himmelfarb and Murrell, 1983; McCallum et al., 1995). Good criterion validity was found when using a cut-off score of 16 to identify persons with major depression in LASA (Beekman et al., 1997). The scale consists of four factors: depressed affect, positive affect, somatic symptoms and interpersonal difficulties (Beekman et al., 1994; Radloff, 1977). Higher values on the depressed affect, somatic symptoms and interpersonal difficulties subscales indicate a greater severity of depressive symptoms, whereas higher scores on the positive affect subscale indicate higher levels of positive affect. Previous studies either provided support for the validity of the 4-factor model (for a meta-analysis see Shafer, 2006), or called into question its validity due to a few items displaying bias or not being in line with the current diagnosis criteria for depression (for a review see Carleton et al., 2013).

The present study included all cognitive tests available in LASA which assessed specific cognitive abilities rather than general cognitive performance.

Episodic memory was assessed using the 15 Words Test, a Dutch version of the Auditory Verbal Learning Test (Rey, 1964). Participants were verbally presented with 15 words which were

repeated over 3 trials. After each trial participants were asked to repeat the words they remembered. Immediate recall performance was determined based on the total score on the three trials. After a distraction period of about 20 min, during which a non-verbal task was performed, participants were asked to name again the words they remembered. This was used as a measure of delayed recall.

Information processing speed was assessed in LASA using an adaptation of the Coding Task (Savage, 1984). Participants were shown two rows of characters, each character in the bottom row belonging to a character in the upper row. This correct letter combination was presented at the top of the page together with two other rows, the upper one containing characters and the lower one being empty. Participants were asked to name the character in the bottom row which belonged to the character in the upper row. They were instructed to respond to the letter combinations as quickly and accurately as possible. The test consisted of three trials of 1 min each and the score on each trial was calculated based on the number of completed combinations. The total score for the three trials was used. The coding task is primarily a measure of information processing speed, but also a global measure of intellectual functioning, as the execution of this task involves various cognitive abilities (i.e., attention, memory function, perceptual organization and speed) (Bouma et al., 1996). Because the original task was adapted to require verbal rather than motor responses, it is considered that the test measures cognitive speed rather than motor speed processes.

Inductive reasoning was assessed using the Raven Colored Progressive Matrices (RCPM) (Raven, 1995). Performance on the RCPM task requires non-verbal and abstract reasoning which are components of fluid intelligence or executive functioning. On each trial participants are presented with a drawing from which a section is missing. They have to identify the correct missing section from six alternative patterns presented at the bottom of the page. Raven consists originally of three subsets: A, Ab and B. Each subset consists of 12 items and a correct response to each item counts for one point. Both items and subsets show a progressive increase in difficulty. Due to time restrictions, only subsets A and B were used in LASA. The omission of the Ab subset is unlikely to affect test performance as pilot studies in LASA have shown that the sum score of A and B subsets correlates strongly ($r=0.96$) with the sum score of A, Ab and B subsets. The sum score of A and B subsets ranged from 0 to 24. Poor performance on this task is considered a good marker of dementia (Gainotti et al., 1992).

Based on previous research (Alexopoulos, 2005; Blazer, 2003; van den Kommer et al., 2013), the following covariates were considered as potential confounders of the association between cognitive abilities and depression symptom dimensions: age (in years), gender, education (in years), number of chronic diseases (based on self reports of the following disorders: chronic non-specific lung disease, cardiac disease, peripheral arterial disease, diabetes mellitus, cerebrovascular accident or stroke, osteoarthritis, rheumatoid arthritis, cancer, and maximum 2 other disorders), alcohol use (no, middle, and high consumption according to the Netherlands Economic Institute index), exercise (total time spent on physical activities in minutes per day), partner status (having a partner or not), use of antidepressant and anxiolytic medication (user versus non-user, based on an inspection of medicine bottles during the medical interview).

2.3. Statistical analysis

All analyses were conducted in MPlus Version 7.1 (Muthén and Muthén, 1998–2012). We used mean and variance-adjusted weighted least squares (WLSMV) estimation which can deal with missing data under the assumption that data are missing at random with respect to covariates included in the model (also

referred to as MARX assumption). Cases with both complete and partially missing data were used to calculate the correlation matrix. WLSMV estimation can be useful in dealing with missing data under the MARX assumption when the percentage of missing data is not substantial (Asparouhov and Muthén, 2014). First, we conducted confirmatory factor analysis (CFA) to examine the fit of a measurement model with four dimensions: depressed affect, positive affect, somatic symptoms, interpersonal difficulties (Beekman et al., 1994; Radloff, 1977). Model fit was evaluated based on the model Chi-square with a *p* value above 0.05 indicating good model fit (Hu and Bentler, 1999); the comparative fit index (CFI) (Bentler, 1990) and the Tucker Lewis index (TLI) (Tucker and Lewis, 1973) with values above 0.90 suggesting acceptable fit, and values above 0.95 indicating a good fit; the root mean square error of approximation (RMSEA) (Steiger, 1990) with values under 0.06 indicating good fit. After establishing the CFA model, we conducted Multiple Indicators Multiple Causes (MIMIC) modelling (Muthén and Muthén, 1998–2012) which simultaneously estimates: a measurement model specifying the relation between CES-D items and latent depression constructs (i.e., CFA model); a regression model whereby latent depression constructs are regressed on several covariates (i.e., age, gender, cognitive abilities); “direct effects” between CES-D items and covariates which inform on differences in item responses due to group membership, despite similar levels of depression severity between groups (see Figure 1). The presence of direct effects indicates measurement non-invariance or differential item functioning (DIF). For instance, in the context of adjustment for gender differences in the severity of depressed affect, males have a lower probability of responding “Yes” to the item “Have you cried at all?”.

Our initial MIMIC model consisted of the CFA measurement model previously established and a regression model estimating the simultaneous effect of age, gender, immediate recall, delayed recall, inductive reasoning and processing speed on CES-D factor means. Because scores on different cognitive measures are positively correlated in the population we took into account their shared variance by simultaneously estimating the effect of all cognitive abilities on CES-D factors. The initial MIMIC model presumed no DIF in any CES-D item and it served as a baseline model for an inspection of modification indices which informed on how much improvement we would gain in model fit by estimating certain DIF effects due to age, gender, or level of performance in the cognitive abilities assessed. This model also informed about the robustness of the CES-D factor structure in the presence of covariates, and about any differences in CES-D factor means due to age, gender and cognitive function levels.

Table 1.
Characteristics of the study sample.

Continuous measures	N	Mean	S.D.	Categorical measures	N	%
Age	3107	70.8	8.8	Sex		
Education	3099	8.8	3.3	Female	1601	52
Chronic diseases	3087	1.4	1.2	Male	1506	48
Physical activity	2889	54.0	69.3	Partner status		
Depressive symptoms	3056	7.97	7.79	With partner	2061	66
Immediate recall	2615	18.4	6.3	Single	1043	34
Delayed recall	2615	5.0	2.8	Antidepressants		
Inductive reasoning	2821	17.7	4.1	User	51	2
Processing speed	2565	71.7	22.7	No user	2620	98
General cognitive ability	3091	26.8	3.2	Anxiolytics		
				User	2507	94
				No user	164	6
				Smoking		
				Never smoked	823	31
				Past smoker	1169	44
				Current smoker	672	25
				Alcohol use		
				None	592	22
				Moderate	1842	69
				Severe	220	8

Note: Age and education were measured in years; physical activity was measured in minutes per day; total scores were used for number of chronic diseases and for cognitive measures; immediate and delayed recall - Auditory Verbal Learning Test; inductive reasoning - Raven Colored Progressive Matrices; processing speed - Coding Task; general cognitive performance - Mini Mental State Examination; depressive symptoms - Center for Epidemiologic Studies Depression Scale.

In a second stage, DIF effects due to age, gender and cognitive function levels were progressively added to the model, starting with the effect leading to the largest improvement in model fit. Model comparison was conducted using a DIFFTEST approach (Muthén and Muthén, 1998–2012) in order to determine whether the adjustment for each additional direct effect resulted in a significant improvement in model fit (i.e., a drop in model Chi square values). Given that the modelling framework involved WLSMV estimation, probit regression coefficients were obtained for direct effects. After adding all significant direct effects to the model, we examined the impact of this adjustment on the association of CES-D factor means with cognitive abilities, age, and gender.

In a third stage, we re-examined the association between CES-D factor means and cognitive abilities (including all direct effects) after adjustment for the effect of eight potential confounders of the association between depression dimensions and cognitive domains: education, number of chronic diseases, alcohol use, exercise, smoking, partner status, use of antidepressant, and use of anxiolytic medication. First, all these covariates were included as predictors in the MIMIC model (alongside with age, gender and cognitive abilities). An additional set of models estimated the effect of one covariate at a time (alongside with the effect of age, gender and cognitive abilities) on depression dimensions in order to determine which covariates could account for the observed associations between cognitive abilities and CES-D depression dimensions.

Because cognitive and depression measures may lack reliability and validity in persons with cognitive impairment or dementia, we conducted sensitivity analyses in a subsample that excluded participants with potential cognitive impairment (i.e., a score of 23 and below on the MMSE).

3. Results

Descriptive statistics for our sample are presented in Table 1. Because our study included data from the baseline LASA cycle, the percentage of missing data was low. Less than 5% of participants had missing data on any one CES-D item, and less than 2% of participants had missing data on the total CES-D score. Sixteen percent of participants had clinically significant depressive symptoms (i.e., a CES-D score of 16 and above). Eleven percent of participants had at least mild to moderate cognitive impairment (i.e., a score of 23 and below on the Mini Mental State Examination).

Confirmatory Factor Analysis was conducted to test a model

Table 2.
CFA model results for CES-D items.

Item no.	Item content	β	S.E.
Depressed affect			
CESD 3	I could not shake off the blues	0.85	0.01
CESD 6	I felt depressed	0.88	0.01
CESD 9	I felt my life was a failure	0.70	0.03
CESD 10	I felt fearful	0.71	0.02
CESD 14	I felt lonely	0.77	0.02
CESD 17	I had crying spells	0.75	0.02
CESD 18	I felt sad	0.84	0.01
Positive affect			
CESD 04	I felt that I was just as good as other people	0.60	0.02
CESD 08	I felt hopeful about the future	0.54	0.02
CESD 12	I was happy	0.85	0.01
CESD 16	I enjoyed life	0.91	0.01
Somatic symptoms			
CESD 01	I was bothered by things that usually don't bother me	0.65	0.02
CESD 02	My appetite was poor	0.57	0.03
CESD 05	I had trouble keeping my mind on what I was doing	0.64	0.02
CESD 07	I felt that everything I did was an effort	0.78	0.01
CESD 11	My sleep was restless	0.56	0.02
CESD 13	I talked less than usual	0.58	0.02
CESD 20	I could not get "going"	0.67	0.02
Interpersonal difficulties			
CESD 15	People were unfriendly	1.00	< 0.01
CESD 19	I felt that people dislike me	0.84	0.03

Note: β =standardized coefficients; All factor loadings are significant at $p < 0.001$.

with 4 factors: somatic symptoms, positive affect, depressed affect, and interpersonal difficulties. CFA results are presented in Table 2. The measurement model showed good fit: Chi square = 1469.53, df 165, $p < 0.001$; CFI = 0.96; TLI = 0.95; RMSEA = 0.05 (95% confidence interval = 0.05–0.05), and all CES-D items loaded well on the hypothesized factors. The depressed affect factor had a correlation of $r = -0.75$ with positive affect, $r = 0.86$ with somatic symptoms, and $r = 0.49$ with interpersonal difficulties. Positive affect had a correlation of $r = -0.69$ with somatic symptoms, and $r = -0.33$ with interpersonal difficulties. Somatic symptoms had a correlation of $r = 0.52$ with interpersonal difficulties. Given that the hypothesized factor structure fitted the data well, this measurement model was included in our MIMIC models.

Our initial MIMIC model results showed that the CFA model for CES-D is robust to external covariates (i.e., cognitive abilities, age and gender). The model fitted the data well: CFI = 0.95; TLI = 0.94; RMSEA = 0.04 (95% confidence interval = 0.04 to 0.04), and factor loadings remained strong and statistically significant (results not presented). Model results suggest that persons with lower levels of inductive reasoning had statistically significant higher levels of depressed affect and somatic symptoms, whereas persons with slower processing speed had statistically significant higher levels of somatic symptoms (see model 1 in Table 4). A marginally significant association was found between processing speed and depressed affect ($B < -0.01$, $p = 0.06$, $\beta = -0.06$), suggesting that slower processing speed was related to higher levels of depressed affect. Females had statistically significant higher levels of depressed affect ($B = 0.42$, $p < 0.001$, $\beta = 0.47$) and somatic symptoms ($B = 0.30$, $p < 0.001$, $\beta = 0.44$), as well as lower levels of positive affect ($B = -0.19$, $p < 0.001$, $\beta = -0.30$). Older persons had statistically significant lower levels of positive affect ($B = -0.01$, $p < 0.01$, $\beta = -0.09$).

In the context of adjustment for the severity of depression symptom dimensions, three items displayed response bias due to gender, indicating that women had a higher probability of reporting crying spells (item 17), sleep disturbance (item 11), and

Table 3.
MIMIC models with direct effects between covariates and CES-D items.

Number of direct effects	chi ² (df)	Δ chi ²	B	S.E.	β
No direct effects	1347 (261)				
1 Age predicts Loneliness (CESD 14)	1313 (260)	41	0.02	< 0.01	0.18
2 Gender predicts Crying (CESD 17)	1293 (259)	23	0.29	0.06	0.29
3 Age predicts Hope (CESD 8)	1278 (258)	18	-0.01	< 0.01	-0.10
4 Gender predicts Sleep (CESD 11)	1265 (257)	15	0.18	0.05	0.18
5 Gender predicts Feeling as good as others (CESD 4)	1252 (256)	14	0.21	0.06	0.21

Note: All direct effects are significant at $p < 0.001$; chi² (df) – model chi squared and the associated degrees of freedom; Δ chi² refers to the difference in chi-square between a model that estimates one additional direct effect and a model that estimates one fewer direct effect; B = non-standardized coefficients; S.E. = standard error; β = standardized coefficients

feeling as good as others (item 4) (see Table 3). Two items displayed response bias due to age, indicating that older persons reported more loneliness (item 14) and less hope about the future (item 8) (see Table 3). We found no DIF due to level of cognitive functioning. DIFFTEST results indicated a significant drop in model Chi square for each additional DIF effect estimated (suggesting an improvement in model fit). Adjusting for DIF effects did not alter conclusions about the associations of CES-D factors with cognitive abilities (see model 2 in Table 4). Lower levels of inductive reasoning remained statistically significant associated with higher levels of depressed affect and somatic symptoms, whereas slower processing speed remained statistically significant associated with higher levels of somatic symptoms. Also, age and gender differences in CES-D factor means remained significant and of similar magnitude after adjusting for DIF (results not presented).

After adjusting for the effects of additional covariates (i.e., education, number of chronic diseases, alcohol use, exercise, smoking, partner status, use of antidepressant and anxiolytic medication), the association between processing speed and somatic symptoms was no longer statistically significant, whereas persons with lower levels of inductive reasoning continued to show higher levels of depressed affect and somatic symptoms (see model 3 in Table 4). Additional analyses were conducted to determine which of the covariates accounted for the observed associations between depression dimensions and cognitive domains. The association between somatic symptoms and processing speed lost statistical significance after accounting for the number of chronic diseases, but it remained significant or marginally significant when adjusting for any of the other covariates. Inductive reasoning remained statistically significant associated with depressed affect and somatic symptoms after adjusting for any of the confounders. Findings from sensitivity analyses conducted in older adults without potential cognitive impairment suggest that the CES-D factor structure, the DIF effects, and the associations between depression-symptom dimensions and cognitive abilities did not change as a result of excluding cognitively impaired persons.

4. Discussion

Using data from a large nationally representative sample of LASA and an analytic strategy that adjusted for the influence of measurement bias, our findings provide partial support for a differential association between depression symptom dimensions and cognitive abilities, while also adding evidence for the measurement invariance of CES-D across age, gender and cognitive function levels in older adults. Consistent with previous studies

Table 4.

Cross-sectional associations between CES-D factors and cognitive abilities.

	Depressed affect			Positive affect			Somatic symptoms			Interpersonal difficulties		
	B	S.E.	β	B	S.E.	β	B	S.E.	β	B	S.E.	β
Model 1. Effect of cognitive abilities on CES-D factors in a model unadjusted for DIF												
Immediate recall	– < 0.01	0.01	–0.03	0.01	< 0.01	0.04	< –0.01	0.01	–0.01	–0.01	0.01	–0.05
Delayed recall	0.01	0.01	0.04	< –0.01	0.01	< –0.01	< 0.01	0.01	0.02	–0.01	0.02	–0.02
Inductive reasoning	–0.03***	0.01	–0.11	< 0.01	0.01	0.01	–0.02***	0.01	–0.12	–0.02	0.01	–0.07
Processing speed	< –0.01	< 0.01	–0.06	< 0.01	< 0.01	0.03	< –0.01*	< 0.01	–0.07	< 0.01	< 0.01	0.04
Model 2. Effect of cognitive abilities on CES-D factors in a model adjusted for DIF												
Immediate recall	– < 0.01	0.01	–0.03	0.01	< 0.01	0.04	< –0.01	0.01	–0.01	–0.01	0.01	–0.05
Delayed recall	0.01	0.01	0.04	< –0.01	0.01	–0.01	< 0.01	0.01	0.02	–0.01	0.02	–0.02
Inductive reasoning	–0.03***	0.01	–0.11	< 0.01	0.01	0.01	–0.02***	0.01	–0.12	–0.02	0.01	–0.07
Processing speed	< –0.01	< 0.01	–0.06	< 0.01	< 0.01	0.03	< –0.01*	< 0.01	–0.07	< 0.01	< 0.01	0.04
Model 3. Effect of cognitive abilities on CES-D factors in models adjusted for DIF and for the effect of additional covariates												
Immediate recall	< –0.01	0.01	–0.02	< 0.01	< 0.01	0.04	< 0.01	0.01	< 0.01	–0.01	0.01	–0.08
Delayed recall	0.02	0.01	0.05	< –0.01	0.01	–0.01	< 0.01	0.01	< –0.01	< 0.01	0.02	0.01
Inductive reasoning	–0.02**	0.01	–0.10	< 0.01	0.01	< –0.01	–0.02***	0.01	–0.11	–0.02	0.01	–0.07
Processing speed	< –0.01	< 0.01	–0.02	< 0.01	< 0.01	0.02	< –0.01	< 0.01	–0.03	< 0.01	< 0.01	0.02

Note:

B=non-standardized coefficients; S.E.=standard error; β=standardized coefficients; for gender the reference group is male; all three models are adjusted for age and gender; additionally, the third model is adjusted for education, number of chronic diseases, alcohol use, smoking, exercise, partner status, use of antidepressant and anxiolytic medication.

* p < 0.05;

** p < 0.01;

*** p < 0.001.

(Radloff, 1977; Shafer, 2006), we found that depression, as measured by CES-D, can be interpreted in terms of four domains: depressed affect, positive affect, somatic symptoms and interpersonal difficulties. Findings from our MIMIC models suggest that depression symptom dimensions are, to some extent, differentially related to cognitive functioning. Higher levels of depressed affect and somatic symptoms were associated with lower levels of inductive reasoning. Higher levels of somatic symptoms were associated with slower processing speed, but this effect was no longer significant after accounting for the number of chronic diseases. Depressed affect was also associated with processing speed but the effect was only marginally significant. Positive affect and interpersonal difficulties were unrelated to any domains of cognitive performance. Although we found differences in response behavior due to age and gender, the magnitude of item response biases was small and did not affect substantive conclusions about the association between depression dimensions and cognitive abilities. These results have some interesting implications which are discussed below.

Our findings that depressed affect and somatic symptoms were similarly associated with inductive reasoning, and that there was a tendency for both symptom dimensions to be associated with processing speed, are consistent with evidence by Baune et al. (2007) suggesting that higher levels of depressed affect and somatic symptoms were associated with poorer performance on tasks assessing speed, attention and executive function. These findings are in agreement with the subcortical-frontal circuit dysfunction model of late-life depression (Butters et al., 2004), and they build upon existing evidence that late-life depression co-occurs with cognitive impairment affecting in particular executive function and processing speed abilities (Lockwood et al., 2002; Sheline et al., 2006). Our finding that processing speed performance was associated with the somatic factor of CES-D (assessing a combination of somatic and motivational symptoms of depression) is consistent with findings from Euro-D studies suggesting a specific association between motivational symptoms of depression and poor processing speed on a verbal fluency task (i.e., naming as many animals as possible in one minute) (Brailean et al., 2015; Castro-Costa et al., 2007). The specific association between somatic/motivational symptoms and slow processing speed may be

due to vascular disease and a disruption of frontal-subcortical pathways (Alexopoulos, 2002; Alexopoulos et al., 1997), or it may suggest psychomotor slowing due to co-morbid medical conditions. The finding that the number of chronic diseases accounted for the association between somatic symptoms and processing speed in our study is not surprising given in light of evidence that chronic diseases are associated with slower processing speed (Comijs et al., 2009), and with an increased risk of depression (Huang et al., 2010). It is of note that depressed affect and somatic symptoms were highly correlated, which may explain their co-occurrence with poor cognitive functioning. Albeit statistically significant, all effects were small, which is possibly due to the inclusion of relatively healthy community dwelling older adults in our study (i.e., only a small percentage of participants met criteria for possible cognitive impairment or clinical depression).

Because scores on different cognitive measures are positively correlated in the population, our models controlled for their mutual variance in order to determine the unique effect of each cognitive ability on depression scores. The finding that recall ability was not associated with scores on any of the depression factors after partialling out the effect of inductive reasoning and processing speed is consistent with evidence that age differences in memory performance are reduced or eliminated when controlling for processing speed (Bunce and Macready, 2005) or for executive function (Clarys et al., 2009). The finding that the interpersonal difficulties and positive affect dimensions were unrelated to any domains of cognitive performance may suggest that these symptoms of depression are less strongly related to brain changes underlying aging-related cognitive decline, or that these dimensions of CES-D may capture constructs that are not core symptoms of depression.

With regard to differential item functioning, our findings suggest that levels of cognitive functioning did not influence the probability of endorsing certain CES-D items. This could be explained by our sample composition in which only 11% of participants showed cognitive impairment. In the absence of genuine differences in the severity of depression dimensions, older persons reported more loneliness and less hope about the future than younger persons. Females were more likely to report feeling as good as others, sleep disturbance, and crying spells. Our findings

are consistent with previous studies reporting a higher probability of endorsing the item “I had crying spells” in women (Callahan and Wolinsky, 1994; Carleton et al., 2013; Yang and Jones, 2007; Yang et al., 2009), and with studies showing higher levels of hopelessness (Christensen et al., 1999), as well as increased loneliness at advanced ages (Dykstra, 2009). The finding that the magnitude of all DIF effects was small and adjusting for these effects did not alter our substantive conclusions suggests that CES-D has similar measurement properties and can be usefully employed across age, gender and cognitive function levels.

A notable strength of this study is the use of an analytic strategy involving latent variables modelling which allows to account for measurement error and to test for DIF effects while simultaneously investigating the effect of multiple predictors (measured continuously or categorically) on CES-D depression dimensions (Woods, 2009). Other study strengths include the large sample size which allowed for adjustment for important confounders of the association between depression symptoms and cognitive functioning, and the dimensional approach to late-life depression. Our study has also a number of limitations. First, the analytic approach employed can only inform on differences in response behavior due to age, gender and cognitive functioning that are constant across levels of depression symptoms (i.e., uniform DIF). Studies using alternative analytic methods (i.e., multi-group models) could examine whether inconsistencies in response behavior occur only at high or at low levels of depression severity (i.e., non-uniform DIF). Second, the cross-sectional context of this investigation cannot inform on the direction of influence between late-life depression dimensions and cognitive functions. Studies employing a longitudinal design are needed to help clarify the extent to which specific symptom dimensions could differentially predict cognitive outcomes in late life. Last but not least, our study assessed cognitive functioning and depressive symptoms on a continuum of severity, with only a small percentage of persons meeting criteria for possible cognitive impairment or clinical depression. Therefore, our conclusions are limited to community dwelling older adults and more research is needed to determine the extent to which our findings can be replicated in clinical samples.

There remains a need for future studies to harmonize depression symptom dimensions derived from factor analytic studies of different depression measures, and to determine the predictive validity of these depression dimensions by examining the extent to which they are differentially related to cognitive outcomes and to other health outcomes in late life. Studies using a bifactor approach (Reise, 2012) could also help disentangle specific dimensions of depression that are independent from a general factor of depression. A better understanding of the association between cognitive functioning and particular symptom dimensions of late-life depression could benefit future research by informing on potential etiological mechanisms underlying the co-morbid manifestation of depression and cognitive impairment, by helping predict cognitive outcomes in patients with specific depression symptom profiles, and by encouraging the development of targeted interventions for depressed older adults.

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Contributors

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Conflict of interest

none.

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***CHAPTER 5: A MULTIPLE INDICATORS MULTIPLE CAUSES MODEL OF
LATE-LIFE DEPRESSION IN LATIN AMERICAN COUNTRIES***

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Research report

A multiple indicators multiple causes model of late-life depression in Latin American countries



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ABSTRACT

Background: The Euro-D depression scale consists of symptom clusters that may be differentially related to demographic and cognitive characteristics in older adults. This hypothesis needs further investigation and the role of measurement bias on substantive conclusions remains to be established.

Method: The study sample comprised 10,405 community-dwelling older adults from six Latin American countries. We applied a Multiple Indicators Multiple Causes (MIMIC) model for a concurrent investigation of measurement bias and of the association between Euro-D symptom clusters and background variables.

Results: The factorial validity of Euro-D, with a two-dimensional structure – affective suffering and motivation disturbance, was consistently supported in all countries. Although complete measurement invariance could not be assumed across countries, measurement bias was minor. Both Euro-D factors were unrelated to age, but related to gender, as well as to impairment in memory and verbal fluency. Gender differences were larger for affective suffering than for motivation disturbance, whereas differences in verbal fluency impairment were more strongly related to motivation disturbance.

Limitations: Our analytic strategies could only examine invariance at the level of indicator thresholds. The generalisability of current findings needs to be examined in clinical populations. A wider set of cognitive tests is needed. We did not examine the compositional factors that could have accounted for the variation in Euro-D scores across countries, as this was beyond the aims of the paper.

Conclusion: The current study adds evidence for the construct validity of Euro-D and for the possible differential association of depression symptom-clusters with gender and verbal fluency in older adults. An understanding of the heterogeneity of late-life depression may carry clinical implications for the diagnosis and treatment of depression in old age.

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1. Introduction

The clinical picture of late-life depression differs in several aspects from that observed in early-life depression. While Major Depressive Disorder (MDD) has a lower prevalence in older adults, subclinical

depressive symptoms are more common in old age (Meeks et al., 2011; Romanoski et al., 1992). Moreover, older individuals are less likely to report depressed mood (Gallo et al., 1994) and more likely to report somatic symptoms, fatigue, appetite loss, concentration difficulties, lack of interest in activities and cognitive disturbance (Fountoulakis et al., 2003; Gallo and Rabins, 1999). Although core symptoms required for a standard diagnosis of Major Depressive Disorder include the presence of depressed mood or the loss of interest in activities, late-life depression may be characterized by a “depression without sadness” syndrome (Gallo and Rabins, 1999). As such, late-life depression may be under-detected and under-treated if clinical assessments focus uniquely on the MDD criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV).

The above findings suggest that factors other than depressed mood are likely to account for the high rates of subclinical depressive symptoms in old age. One such factor could be the presence of

Abbreviations: MIMIC, multiple indicators multiple causes; MDD, major depressive disorder; DSM, diagnostic and statistical manual of mental disorders; PCA, principal components analysis; CFA, confirmatory factor analysis; GMS, geriatric mental state; CERAD, consortium to establish a registry for Alzheimer's disease; SEM, structural equation modelling; WLSMV, weighted least squares mean and variance-adjusted; CFI, comparative fit index; TLI, tucker lewis index; RMSEA, root mean square error of approximation; DIF, differential item functioning

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cognitive impairment, with older individuals showing pronounced executive function deficits, slower processing speed and concentration difficulties (Butters et al., 2004). It was suggested that ageing-related dysfunctions of fronto-striatal structures and cerebrovascular disease may precipitate late-life depressive symptoms (Alexopoulos et al., 2005; Alexopoulos et al., 2002). The clinical manifestations of these dysfunctions include executive function/verbal fluency impairment, as well as depression-like symptoms (e.g., reduced interest in activities).

Psychometric studies have provided factor analytic evidence that DSM-III symptoms of depression tend to cluster into two dimensions: disturbance of mood/affective suffering (e.g., depressed mood, tearfulness) and disturbance of motivation (e.g., lack of interest, poor concentration) (Forsell et al., 1994). Similar depression domains have been reported by factor analytic studies of Euro-D, a scale developed to assess symptoms of depression in older adults (Castro-Costa et al., 2007; Prince et al., 1999a; Veropoulou and Tsimbos, 2007). Furthermore, these studies showed that the two Euro-D domains were differentially associated with demographic variables and cognitive function levels. For instance, whereas females reported higher levels of affective suffering than males, this was not the case for motivation symptoms. This finding is consistent with a large body of literature that documented gender differences in mood disturbances (Djernes, 2006; Inaba et al., 2005; Mirowsky, 1996). Furthermore, while the severity of motivation symptoms increased with age, the severity of affective suffering symptoms did not. Also, a positive association was found between verbal fluency impairment and the severity of motivation symptoms, but not affective suffering symptoms. Memory impairment was unrelated to either symptom clusters. Taken together, these findings provided indirect support for the “depression-executive dysfunction hypothesis” which posits that late-life depression can present as motivation-related symptoms driven by ageing-related decline in executive function (Alexopoulos, 2005). Given that the distinction between affective suffering and motivation symptoms may carry clinical implications for the diagnosis and treatment of depression in old age, this hypothesis warrants further investigation.

The assessment of depressive symptoms across geographical regions requires instruments that are culturally-valid. Cultural beliefs can influence response behaviours leading to biased estimates of group differences in trait levels. An instrument is culturally invariant when individuals from different cultures have similar probabilities of item endorsement. A study that investigated the invariance of Euro-D across European countries suggested that the affective suffering factor is better characterised and more invariant across European countries than the motivation factor (Castro-Costa et al., 2008). Further investigation is needed to assess the validity of Euro-D in low and middle income countries.

This study aimed:

- to establish the factor structure of Euro-D across six Latin American countries;
- to determine whether measurement bias has weakened or exaggerated any differences in depression functioning between countries, gender, age and cognitive function levels;
- to test previous hypotheses of a differential association of depression domains with age, gender, verbal fluency and memory performance.

2. Method

2.1. Participants

The study sample consisted of 10,405 older adults from six Latin American countries (Peru, Venezuela, Mexico, Puerto Rico, Cuba, Dominican Republic) who took part in the first wave of

population-based surveys conducted by the 10/66 Dementia Research Group (Prince et al., 2007). All participants included in this study were at least 65 years old and had no diagnosis of dementia. Participants from Peru and Mexico were recruited from both urban and rural catchment areas, while participants from the other four countries were only recruited from urban areas. Studies were approved by local ethical committees in each country, and by the King's College London Research Ethics Committee. All individuals who took part in the surveys provided an informed consent. Interviews were conducted by trained individuals and were usually carried out in the interviewees' homes in a single session that lasted two to three hours.

2.2. Measures

The EURO-D (Prince et al., 1999b) is a scale developed from the Geriatric Mental State (GMS; Copeland et al., 1976) with the aim to assess 12 symptoms of late-life depression: depressed mood, pessimism, suicidality, guilt, sleep, interest, irritability, appetite, fatigue, concentration, enjoyment and tearfulness. Scores range from 0 to 12, with higher scores indicating greater symptom severity. Good internal consistency and criterion validity have been reported for this instrument (Prince et al., 1999b). A score of 4/5 or above has been reported as the optimal cut-off point for the identification of probable depression cases (Castro-Costa et al., 2007; Guerra et al., 2015). Principal component analysis (PCA) and confirmatory factor analysis have revealed that a two-factor solution-affective suffering and motivation-fits the data well across European countries (Castro-Costa et al., 2008; Prince et al., 1999a; Prince et al., 1999b), Latin American countries and India (Prince et al., 2004). Across European countries, stronger measurement invariance was found for the affective suffering factor than the motivation factor (Castro-Costa et al., 2008).

Assessments of cognitive function included the delayed recall of a 10-word list and the animal naming verbal fluency task adapted from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Vanderhill et al., 2011). The delayed recall task required participants to recall 10 words that had been previously presented three times during the learning phase. The animal naming verbal fluency task required participants to name as many animals as possible over a period of 1 min. Performance on the verbal fluency task is thought to rely upon multiple cognitive processes such as semantic memory, language ability, and executive function components (Abwender et al., 2001; Henry and Phillips, 2006). Additionally, we used measures of age, gender and country of residence.

2.3. Statistical analysis

Structural Equation Modelling (SEM) analyses were conducted in MPlus Version 7.2 (Muthén and Muthén, 1998–2012) using mean and variance-adjusted weighted least squares (WLSMV) estimation. WLSMV is well suited for modelling categorical or ordered data and does not assume normally distributed variables (Brown, 2006). Confirmatory factor analysis was conducted to test a model with two first-order factors (affective suffering and motivation). Drawing upon previous factor analytic findings (Prince et al., 1999b), we hypothesised that loss of interest, lack of enjoyment and poor concentration should load on the motivation factor, whereas the other nine Euro-D items should load on the affective suffering factor. The model was tested in each Latin American country separately as well as in the pooled sample. Model fit was evaluated based on commonly adopted standards. Conventionally, a Chi-square index with a *P*-value above 0.05 shows good model fit, indicating a small discrepancy between the sample covariance matrices and the covariance matrices predicted

by the model (Hu and Bentler, 1999). However, because Chi-Square statistic is sensitive to sample size, the model is nearly always rejected when large samples are used (Bentler and Bonett, 1980). Therefore, the comparative fit index (CFI; Bentler, 1990), and the Tucker Lewis index (TLI; Tucker and Lewis, 1973) were also used when evaluating model fit. Values above 0.90 were considered an acceptable fit, and above 0.95 a good fit. The root mean square error of approximation (RMSEA; Steiger, 1990) should have values below 0.10 for acceptable fit, and below 0.05 for good fit. Modification indices, which are derived from model Chi-square, were examined to decide whether additional parameters should be estimated to improve model fit.

After evaluating the measurement model, we proceeded to testing the validity of the model in the presence of covariates using Multiple Indicators Multiple Causes (MIMIC) modelling. MIMIC consists of a measurement model (established at the CFA stage), as well as a structural model. The structural model specifies the effect of the covariates/grouping variables on factors, thereby estimating group difference in latent factor means. The structural model can also include direct effects of the covariates on indicators, holding the latent variables constant. A significant direct effect indicates differential item functioning (DIF). DIF is present when response probabilities to an item differ between groups, despite the fact that groups have been matched for levels of the latent variables. For instance, if males have a lower probability than females of responding “Yes” to the item “Have you cried at all?”, despite similar levels of affective suffering, the item is considered to have gender DIF. The presence of DIF undermines measurement invariance. Conversely, measurement invariance is concluded when the probability of endorsing an item is comparable between groups, given similar levels of the latent trait score.

The following covariates were included in our model: country, gender, age, verbal fluency and delayed recall. Female gender was used as the reference group in all analyses. Dummy variables were created to allow for country comparisons and Cuba was used as the reference group as it has the largest sample size. A step-wise forward approach was used to assess the direct effects. To decide which direct path should be first added to the model, we examined the magnitude of the modification indices. Each modification index suggests how much the model could be improved by estimating an additional parameter (e.g., direct path). The modification index with the highest magnitude suggests the direct path that could be added to the model for the best improvement in model fit. Accordingly, we added the direct path with the highest modification index and compared this model with the simpler model which contained no direct path. A DIFFTEST (Muthén and Muthén, 1998–2012) was conducted to determine whether adding the direct path resulted in a significant improvement in model fit. Conventionally, a χ^2 difference with a *P*-value below 0.05 indicates that the model that estimates the direct path fits the data better than the simpler model; therefore, the more complex model should be retained. Conversely, a *P*-value larger than 0.05 suggests that the estimation of the direct path does not result in a significant improvement in model fit; therefore, the simpler model should be retained. Direct paths can be added to the model until the inclusion of a new path does no longer result in a significant improvement in model fit. However, given our large sample size, DIFFTEST results are likely to be significant even when they reflect trivial improvement in model fit. Therefore, the number of direct paths included in our final model was determined after an examination of the practical impact of the DIFFTEST results. Specifically, we examined the magnitude of the direct effects, and the impact of the direct paths estimation on conclusions about group differences in factor means. Any improvement in model fit, albeit statistically significant, would have a trivial impact on our model results when the magnitude of the direct effects is very small and

the size of the estimate of group differences in factor means remains largely unchanged. Furthermore, we examined the correlation between factor scores before and after adding each direct path. A correlation of almost one between factor scores suggests that the estimation of additional direct paths does not change the model in important ways.

3. Results

3.1. Descriptive statistics

Across variables, an overall 2.21% of data were missing. Descriptive statistics per country and in the overall sample are presented in Table 1. The overall sample consisted of a female majority, had a mean age of 74 years, an average score of 4.7 on delayed recall and an average score of 15.8 on verbal fluency. Country-specific proportions of individuals reporting the 12 Euro-D items are also presented in Table 1. Mean Euro-D scores varied from 1.7 in Puerto Rico to 2.9 in Dominican Republic. The proportion of EURO-D scores with a value of 4 or above varied from 16.3% in Puerto Rico to 36.4% in Dominican Republic (Castro-Costa et al., 2007).

3.2. Confirmatory factor analysis

Confirmatory factor analysis was applied to the pooled sample from all countries to test a model with 2 first-order factors. Table 2 shows the country-level and pooled sample CFA results, including goodness-of-fit indices, factor loadings and factor correlations. This measurement model showed good fit in each of the countries as well as in the pooled sample (CFI=0.964; TLI=0.955; RMSEA=0.005). In general, Euro-D items loaded well on the hypothesized factors. The factor correlation was $r=0.66$ in the overall sample and it ranged from $r=0.55$ in Peru to $r=0.77$ in Cuba.

3.3. Multiple Indicators Multiple Causes (MIMIC) model

After adding the covariates, model fit declined but remained within acceptable ranges and factor loadings remained strong and significant (see Table 2 and Fig. 1). Modification indices suggested that model fit could be improved by freely estimating certain direct effects between the covariates and the indicators. We started by adding to the model the direct path with the highest potential to improve model fit and compared this model with the simpler model which contained no direct paths. A step-wise forward procedure was implemented until 10 direct paths between items and covariates were estimated (see Table 3). Nine of the 10 direct paths indicated differences in response behaviour across countries, the majority of which highlighted differences between Cuba and Peru. One direct path was related to gender, with males being more likely to report “irritability” than females. Most of the direct paths involved affective suffering items; only one direct path involved a motivation item (i.e., concentration). DIFFTEST results indicated a significant drop in χ^2 for each additional direct path estimated. The magnitude of all direct effects was small (see Table 3 for standardized coefficients). We examined whether the estimation of each direct path led to changes in the size of the estimate of group differences in factor means. Specifically, we compared results of a model with no direct paths with a model with 5 direct paths and a model with 10 direct paths (see Table 4). The size of the estimates of group differences in factor means remained largely (e.g., males versus females) similar when estimating additional direct paths (see Table 4). Furthermore, an almost perfect correlation was found between factor scores derived before and after adding each direct path (e.g., adding the direct path from the country covariate “Peru” to the item “pessimism” resulted in a correlation of $r=1.000$, $P<0.0001$ for affective suffering, and $r=0.991$, $P<0.0001$ for motivation). Taken together,

Table 1
Demographic characteristics, cognitive function, and Euro-D item responses by country and overall sample.

	Cuba (n=2358)	DR (n=1592)	Peru (n=1589)	Venezuela (n=1638)	Mexico (n=1640)	Puerto Rico (n=1588)	Total (n=10,405)
Female (%)	64.6	65.2	60.1	63.9	62.7	67.5	64.0
Age	74.3(6.7)	74.5(7.1)	74.1(7.0)	72.0(6.5)	73.6(6.2)	75.4(6.8)	74.0(6.8)
Verbal fluency	16.6(5.9)	13.8(4.7)	17.0(5.4)	18.3(6.4)	14.8(4.9)	14.2(4.3)	15.8(5.6)
Delayed recall	5.1(1.9)	4.2(1.9)	4.7(2.0)	5.1(2.1)	4.3(1.9)	4.4(2.0)	4.7(2.0)
Euro-D symptoms (%)							
Depression	40	50	44	39	40	39	42
Pessimism	25	22	14	24	28	11	21
Wish death	14	14	8	8	13	8	11
Guilt	3	5	10	5	8	7	6
Sleep	34	39	22	35	27	23	30
Interest	8	17	10	9	6	3	9
Irritability	18	20	34	26	24	14	22
Appetite	9	19	11	10	13	9	12
Fatigue	17	35	33	30	28	20	26
Concentration	8	15	23	19	12	6	13
Enjoyment	8	18	7	6	5	2	8
Tearfulness	22	39	32	30	33	25	30
Total Euro-D	2.0(2.3)	2.9(2.6)	2.5(2.2)	2.4(2.3)	2.3(2.2)	1.7(2.0)	2.3(2.3)
Depression case Cut-off score ≥ 4 (%)	22.6	36.4	27.3	26.3	26.0	16.3	25.6

Note: Means and standard deviations are presented unless otherwise stated.

Table 2
Factor loadings, factor correlation and fit indices by country (CFA) and overall sample (CFA and MIMIC).

Euro-D items	Cuba (n=2357)	DR (n=1592)	Mexico (n=1640)	Venezuela (n=1638)	Puerto Rico (n=1588)	Peru n=1588	Overall sample (N=10,403)	Overall sample (MIMIC) (N=10,372)
<i>Affective suffering factor</i>								
Depression	0.98	0.88	0.94	0.97	0.97	0.92	0.93	0.93
Pessimism	0.73	0.54	0.60	0.51	0.76	0.61	0.62	0.64
Wishing death	0.78	0.76	0.62	0.61	0.71	0.68	0.71	0.71
Guilt	0.45	0.43	0.36	0.37	0.52	0.52	0.42	0.46
Sleep	0.55	0.62	0.52	0.57	0.53	0.55	0.56	0.56
Irritability	0.37	0.57	0.36	0.45	0.57	0.26	0.41	0.45
Appetite	0.58	0.51	0.40	0.42	0.48	0.50	0.50	0.49
Fatigue	0.66	0.61	0.53	0.52	0.52	0.47	0.57	0.58
Tearfulness	0.88	0.80	0.82	0.84	0.90	0.80	0.84	0.85
<i>Motivation factor</i>								
Interest	0.95	0.91	0.73	0.92	0.90	0.95	0.93	0.93
Concentration	0.59	0.47	0.55	0.59	0.65	0.60	0.56	0.59
Enjoyment	0.94	0.93	0.80	0.99	0.95	0.93	0.95	0.96
Factor correlation	0.77	0.66	0.73	0.68	0.72	0.55	0.68	0.66
<i>Model fit</i>								
χ^2 (df)	378(53)	278(53)	251(52)	361(53)	250(53)	279(53)	1551(53)	3351(143)
RMSEA	0.051	0.052	0.048	0.060	0.048	0.052	0.052	0.047
(90% CI)	(0.046–0.056)	(0.046–0.058)	(0.042–0.054)	(0.054–0.065)	(0.042–0.054)	(0.046–0.058)	(0.050–0.054)	(0.045–0.048)
CFI	0.976	0.963	0.966	0.960	0.971	0.954	0.964	0.913
TLI	0.970	0.954	0.957	0.950	0.964	0.943	0.955	0.894

these findings suggest that any bias due to differential item functioning is minimal and that accounting for it has trivial consequences on model results. Accordingly, although the estimation of additional direct paths could have resulted in an additional improvement in model fit, we decided to limit our final model to 10 direct paths.

The effects of the covariates on latent mean scores are presented as unstandardised and standardised coefficients in Table 4. For the model with no direct paths, when examining country

differences in affective suffering levels, we found that Dominican Republic, Peru, Venezuela and Mexico had significantly higher scores than Cuba, while Puerto Rico had significantly lower scores than Cuba. For motivation disturbance levels, we found that, compared to Cuba, scores were significantly higher in Dominican Republic, Peru and Venezuela, while they were significantly lower in Mexico and Puerto Rico. Gender differences were also found, with female participants having significantly higher levels of both

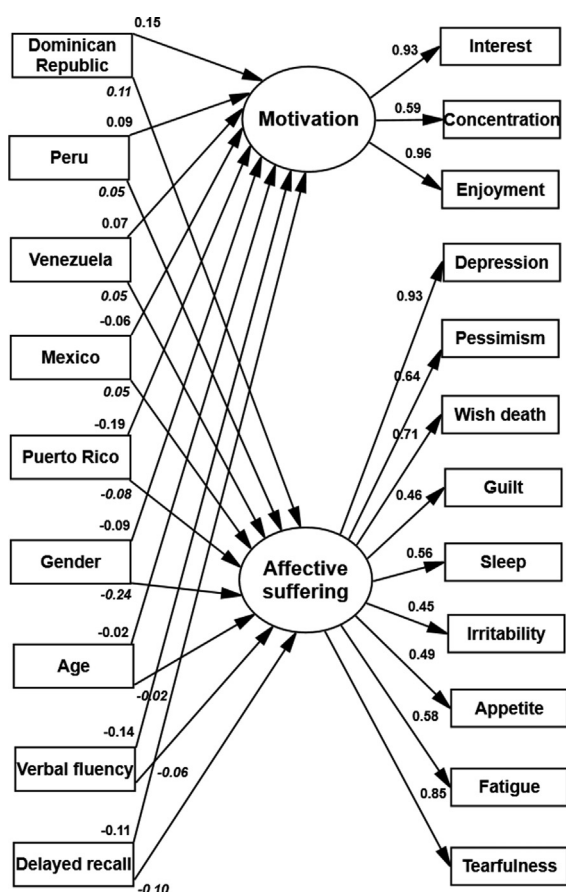


Fig. 1. Multiple Indicator Multiple Causes (MIMIC) model showing the impact of background variables on the two factors, before adjusting for direct effects. Residual covariances are not shown in the model. For gender the reference group is female; for country the reference group is Cuba.

affective suffering and motivation than male participants. The magnitude of the gender differences was larger for affective suffering ($\beta = -0.24$) compared to motivation ($\beta = -0.09$). Age did not have a significant effect on either motivation or affective suffering levels. Participants with higher levels of verbal fluency had significantly lower affective suffering ($\beta = -0.06$) and motivation disturbance levels ($\beta = -0.14$). Participants with higher levels of delayed recall had lower levels on both affective suffering ($\beta = -0.11$) and motivation ($\beta = -0.10$).

3.4. Sensitivity analysis

At the CFA stage modification indices suggested that model fit could be improved by estimating several more parameters. However, given that our initial measurement model had a good fit, we decided not to add additional parameters to the model. Our decision was motivated by the rationale that simpler models are more parsimonious and more likely to be replicated in different datasets (Crowley and Fan, 1997). However, to check the robustness of our conclusions, we performed a sensitivity analysis by estimating additional parameters (e.g., correlating residuals between “depression” and “tearfulness” items). This resulted in a slight improvement in model fit but did not alter model results regarding factor loadings, DIF effects, or the magnitude and direction of group differences in factor means. Similarly, at the MIMIC stage we decided to stop the step-wise forward estimation after the first 10 direct paths were added to the model. This decision was motivated by our findings suggesting a trivial impact

on model results despite a statistically significant improvement in model fit.

Our results showed that age was not significantly related to either affective suffering or motivation. However, previous studies (Castro-Costa et al., 2007; Forsell et al., 1994) have suggested that the effect of age on motivation may be confounded by cognitive function levels. To test this hypothesis, we conducted post hoc analyses where we eliminated cognitive variables from our MIMIC model. When eliminating only the memory variable from the model, the effect of age on both affective suffering ($\beta = 0.03$; $P = 0.80$) and motivation ($\beta < 0.01$; $P = 0.98$) remained non-significant¹. When eliminating only the verbal fluency variable, the effect of age on both affective suffering ($\beta = -0.09$; $P = 0.43$) and motivation ($\beta = -0.05$; $P = 0.74$) remained non-significant. When eliminating both cognitive variables from the analysis, older age was related to significantly higher levels of motivation disturbance ($\beta = 0.39$; $P < 0.05$) and affective suffering ($\beta = 0.26$; $P < 0.05$). Albeit statistically significant, the effect of age on Euro-D factors was small and it should be noted that we did not correct for multiple comparisons in our analyses. There is hence some support that cognitive function levels may confound the effects of age on both affective suffering and motivation.

4. Discussion

Using data from population-based surveys our study adds evidence for the construct validity of Euro-D in Latin American countries, a world region that faces unprecedented rates of demographic ageing and growing ageing-related health care costs (Alzheimer's Disease International, 2009). Hypotheses were tested using an analytic strategy where the influence of any measurement bias would have been adjusted for and where the ordinal nature of item responses was appropriately accounted for.

We found support for previous findings that depression, as measured by Euro-D, can be interpreted in terms of two domains: affective suffering and motivation (Castro-Costa et al., 2007; Prince et al., 1999a; Prince et al., 1999b). In contrast to the study by (Castro-Costa et al., 2008) which suggested that the affective suffering factor had stronger measurement invariance than the motivation factor across European countries, our results indicate that Latin American countries differ more in their response behaviour to affective suffering items than motivation items. Moreover, we found that males are more likely to report irritability than females, in the absence of genuine gender differences in affective suffering levels. However, measurement non-invariance was not substantial. This conclusion was guided by findings of weak direct effects, as well as almost perfect correlations between factor scores derived before and after having added the direct effects. Also, adjusting for direct effects did not alter our conclusions about group differences in factor means. Taken together, these findings suggest that Euro-D has good construct validity and can be appropriately used for cross-cultural comparisons, as well as across age groups, gender and levels of cognitive impairment.

Our findings regarding gender differences are in line with previous studies that reported significantly higher levels of affective suffering in female compared to male participants (Castro-Costa et al., 2007; Forsell et al., 1994; Prince et al., 1999a). Although we also found that females had higher levels of motivation than males, the magnitude of the gender difference was much larger for affective suffering.

In contrast to previous studies that reported a significant positive association between age and motivation, but not affective

¹ β coefficients for age are presented per 10 years.

Table 3Alternative MIMIC models with direct effects between covariates and items estimated in a stepwise process ($N=10,372$).

Model	χ^2 (df)	$\Delta\chi^2$ (df)	CFI	TLI	RMSEA (90% CI)	B	S.E.	β
1 No direct effects	3351 (143)		0.913	0.894	0.047 (0.045–0.048)			
2 + Peru → Concentration	3229 (142)	155	0.916	0.897	0.046 (0.044–0.047)	0.672	0.055	0.231
3 + Peru → Pessimism	3102 (141)	153	0.920	0.901	0.045 (0.044–0.046)	–0.567	0.046	–0.197
4 + Peru → Sleep	2972 (140)	120	0.923	0.905	0.044 (0.043–0.046)	–0.532	0.043	–0.187
5 + Peru → Wishing death	2873 (139)	105	0.926	0.907	0.044 (0.042–0.045)	–0.594	0.055	–0.207
6 + Male → Irritability	2769 (138)	104	0.929	0.910	0.043 (0.041–0.044)	0.297	0.029	0.141
7 + Concentration → Venezuela	2679 (137)	110	0.931	0.912	0.042 (0.004–0.044)	0.577	0.057	0.198
8 + Fatigue → Venezuela	2590 (136)	122	0.933	0.915	0.042 (0.040–0.043)	0.454	0.043	0.161
9 + Pessimism → Puerto Rico	2495 (135)	158	0.936	0.918	0.041 (0.040–0.042)	–0.510	0.046	–0.174
10 + Depression → Peru	2403 (134)	86	0.938	0.920	0.040 (0.039–0.042)	–0.496	0.040	–0.171
11 + Fatigue → Dominican Republic	2334 (133)	63	0.940	0.922	0.040 (0.039–0.041)	0.398	0.043	0.138

Notes: $\Delta\chi^2$ =DIFFTEST; B=unstandardised estimate; S.E.=standard error; β =standardised estimate; All χ^2 , $\Delta\chi^2$ and β values are significant at $P < 0.0001$.

Table 4

Impact of country, gender, age, verbal fluency and delayed recall on the affective suffering and motivation factors.

	Model with no direct paths				Model with 5 direct paths				Model with 10 direct paths			
Affective suffering	B	S.E.	P-value	β	B	S.E.	P-value	β	B	S.E.	P-value	β
Dominican Republic	0.283	0.037	< 0.001	0.105	0.281	0.037	< 0.001	0.103	0.225	0.037	< 0.001	0.081
Peru	0.143	0.036	< 0.001	0.053	0.401	0.037	< 0.001	0.148	0.607	0.043	< 0.001	0.220
Venezuela	0.144	0.036	< 0.001	0.054	0.144	0.036	< 0.001	0.054	0.077	0.037	< 0.05	0.028
Mexico	0.132	0.036	< 0.001	0.049	0.132	0.036	< 0.001	0.049	0.132	0.036	< 0.001	0.048
Puerto Rico	–0.217	0.039	< 0.001	–0.080	–0.216	0.039	< 0.001	–0.079	–0.147	0.039	< 0.001	–0.053
Gender	–0.477	0.024	< 0.001	–0.235	–0.509	0.024	< 0.001	–0.250	–0.514	0.024	< 0.001	–0.248
Age	–0.030	0.002	0.124	–0.180	–0.030	0.002	0.119	–0.180	–0.030	0.002	0.115	–0.190
Verbal fluency	–0.011	0.002	< 0.001	–0.061	–0.011	0.002	< 0.001	–0.061	–0.011	0.002	< 0.001	–0.060
Delayed recall	–0.049	0.006	< 0.001	–0.102	–0.049	0.006	< 0.001	–0.101	–0.049	0.006	< 0.001	–0.100
Total variance explained	9%				11%				12%			
Motivation	B	S.E.	P-value	β	B	S.E.	P-value	β	B	S.E.	P-value	β
Dominican Republic	0.397	0.047	< 0.001	0.146	0.396	0.047	< 0.001	0.146	0.396	0.047	< 0.001	0.146
Peru	0.245	0.051	< 0.001	0.090	0.031	0.054	0.570	0.011	0.031	0.054	0.570	0.011
Venezuela	0.196	0.051	< 0.001	0.073	0.195	0.051	< 0.001	0.073	0.018	0.055	0.746	0.007
Mexico	–0.154	0.054	< 0.01	–0.057	–0.155	0.054	< 0.01	–0.058	–0.157	0.054	< 0.01	–0.059
Puerto Rico	–0.519	0.062	< 0.001	–0.190	–0.520	0.063	< 0.001	–0.191	–0.522	0.063	< 0.001	–0.192
Gender	–0.174	0.033	< 0.001	–0.085	–0.174	0.033	< 0.001	–0.086	–0.174	0.033	< 0.001	–0.086
Age	–0.040	0.002	0.131	–0.240	–0.040	0.002	0.131	–0.240	–0.040	0.002	0.131	–0.250
Verbal fluency	–0.024	0.003	< 0.001	–0.137	–0.024	0.003	< 0.001	–0.137	–0.024	0.003	< 0.001	–0.138
Delayed recall	–0.055	0.008	< 0.001	–0.111	–0.055	0.008	< 0.001	–0.112	–0.055	0.008	< 0.001	–0.112
Total variance explained	12%				11%				12%			

Notes: For gender the reference group is female; for country the reference group is Cuba; B and β coefficients for age are presented per 10 years; verbal fluency coefficients are presented per animal named; delayed recall coefficients are presented per word recalled.

suffering (Castro-Costa et al., 2007; Prince et al., 1999a), our findings show that age was not a significant predictor of either motivation or affective suffering. Of note, individuals with dementia were excluded from our analysis, which was not possible in the SHARE study analysis (Castro-Costa et al., 2007). Current findings should be interpreted in the context where any age differences in motivation and affective suffering levels have been adjusted for the effect of cognitive function (as well as for the effect of other covariates). When cognitive variables were excluded from our model, age became significantly related to both affective suffering and motivation levels. This is in line with previous studies (Castro-Costa et al., 2007; Forsell et al., 1994) which suggested that cognitive function levels may confound the effect of age on depression dimensions.

Better performance on verbal fluency and delayed recall tasks was significantly but weakly related to lower levels of both affective suffering and motivation symptoms. However, in line with findings by Castro-Costa et al. (2007), our study shows a stronger relative magnitude of the association between verbal

fluency and motivation disturbance, compared to affective suffering.

5. Limitations

In the current study we opted for MIMIC modelling because this method allows for the concurrent investigation of the effect of multiple variables, measured categorically or continuously, on the factor model. Although MIMIC modelling is a robust method in the detection of non-invariance at the level of factor means and indicator intercepts, this method has its limitations. For instance, MIMIC modelling can only detect group differences in item thresholds (uniform DIF), but not group differences in item discrimination (non-uniform DIF) (Woods et al., 2009). Thus, our study assumed group differences in response behaviour that are constant across levels of affective suffering or across levels of motivation. Future investigation could explore whether inconsistencies in response behaviour occur at high/low levels of affective suffering/motivation by using an alternative method:

multi-group factor analysis. A second limitation is that our findings are only relevant to general community-dwelling populations without probable dementia. Further research is needed to examine the generalisability of current findings to clinical populations. Another limitation is that our conclusions were based only on two measures of cognitive function (i.e. verbal fluency and delayed recall). A wider set of cognitive tests would be needed for a more comprehensive understanding of the differential associations between cognitive function and depressive symptoms in the elderly. Also, the question of whether there is a “depression without sadness” syndrome in the elderly has to be addressed beyond the cross-sectional context of the current investigation. Last but not least, the question of what compositional factors might be accounting for the variation in Euro-D scores and in the prevalence of depression cases across countries remains unexplored in the present paper. This question is worth addressing in future studies with a broader framework of variables that could explain the differences in depressive symptoms across countries. The primary aim of our paper was to investigate the validity of Euro-D and to examine group differences in depression domains. Our study has identified, to some extent, what is not contributing to the difference in Euro-D scores and in the prevalence of depression cases across countries (i.e. measurement bias/differential item functioning).

6. Conclusions

The current study extends previous investigations in several ways. First, our findings add support for the cross-cultural validity of Euro-D depression scale in Latin American countries. Second, the present study provides support for previous findings that Euro-D domains may be differentially associated with cognitive function levels and demographic characteristics in older adults. Greater severity of both affective suffering and motivation was related to female gender and to higher impairment in verbal fluency and memory. Gender differences were larger for the affective suffering factor, whereas individual differences in verbal fluency were more strongly associated with the motivation factor. Age was unrelated to either depression domain when cognitive function levels were controlled for. When cognitive function levels were not adjusted for, older age was related to both affective suffering and motivation disturbance. Third, we found that measurement bias was minor and did not alter substantive conclusions about the association of depression domains with demographic characteristics and cognitive function levels.

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The funding sources had no involvement in the conduct of research or in the preparation of the article.

Conflict of interest

none.

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***CHAPTER 6: LONGITUDINAL ASSOCIATIONS BETWEEN LATE-LIFE
DEPRESSION DIMENSIONS AND COGNITIVE FUNCTIONING: A CROSS-
DOMAIN LATENT GROWTH CURVE ANALYSIS***

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Longitudinal associations between late-life depression dimensions and cognitive functioning: a cross-domain latent growth curve analysis

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Background. Cognitive impairment and depression often co-occur in older adults, but it is not clear whether depression is a risk factor for cognitive decline, a psychological reaction to cognitive decline, or whether changes in depressive symptoms correlate with changes in cognitive performance over time. The co-morbid manifestation of depression and cognitive impairment may reflect either a causal effect or a common cause, depending on the specific symptoms experienced and the cognitive functions affected.

Method. The study sample comprised 1506 community-dwelling older adults aged ≥ 65 years from the Longitudinal Aging Study Amsterdam (LASA). We conducted cross-domain latent growth curve analyses to examine longitudinal associations between late-life depression dimensions (i.e. depressed affect, positive affect, and somatic symptoms) and specific domains of cognitive functioning (i.e. processing speed, inductive reasoning, immediate recall, and delayed recall).

Results. Poorer delayed recall performance at baseline predicted a steeper increase in depressed affect over time. Steeper decline in processing speed correlated with a steeper increase in somatic symptoms of depression over time.

Conclusions. Our findings suggest a prospective association between memory function and depressed affect, whereby older adults may experience an increase in depressed affect in reaction to poor memory function. Somatic symptoms of depression increased concurrently with declining processing speed, which may reflect common neurodegenerative processes. Our findings do not support the hypothesis that depression symptoms may be a risk factor for cognitive decline in the general population. These findings have potential implications for the treatment of late-life depression and for the prognosis of cognitive outcomes.

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Key words: Cognitive abilities, cognitive ageing, depression symptom dimensions, late-life depression, latent growth curve models.

Introduction

Extensive evidence suggests that late-life depression co-occurs with cognitive dysfunctions affecting in particular fluid cognitive abilities such as processing speed, executive function, and episodic memory (e.g. Comijs *et al.* 2001; Lockwood *et al.* 2002; Baudic *et al.*

2004; Sheline *et al.* 2006; Morimoto & Alexopoulos, 2013; Koenig *et al.* 2014). However, the direction of influence remains unclear, leaving an unresolved question of whether depression is a risk factor for cognitive impairment, a psychological reaction to cognitive impairment, or a prodromal syndrome of dementia.

To overcome problems of reversed causation, a number of studies have investigated bi-directional prospective associations between depression symptoms and cognitive functioning. Some studies found that higher baseline levels of depressive symptoms predicted steeper decline in general cognitive performance

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in persons aged 60–80 years (Gale *et al.* 2012), steeper decline in delayed recall and global cognitive function in persons aged 65–84 years (Panza *et al.* 2009), as well as slower processing speed and reaction time at follow-up in persons aged 70–97 years (Bunce *et al.* 2014), whereas baseline cognitive performance did not predict changes in depressive symptoms over time. Other studies found evidence for the opposite direction of the effect whereby poorer attention and episodic memory in persons aged ≥ 85 years (Vinkers *et al.* 2004), poorer episodic memory in persons aged ≥ 50 years (Jajodia & Borders, 2011), and poorer global cognitive performance in persons aged ≥ 70 years (Perrino *et al.* 2008) predicted an increase in depression symptoms over time, whereas baseline depression levels were unrelated to the rate of cognitive decline. A study by van den Kommer *et al.* (2013) found evidence for both directions of the effect whereby higher depression symptoms at baseline predicted steeper decline in processing speed and general cognitive ability over time, and slower processing speed at baseline predicted an increase in depression symptoms over time in persons aged 55–85 years. The same study by van den Kommer *et al.* (2013) found no significant association between the course of depressive symptoms and the course of general cognitive functioning or processing speed. The mixed evidence regarding the longitudinal association between depression symptoms and cognitive functioning in late life may be due to methodological differences between studies such as the number of assessment waves included, the length of follow-ups, the age range of participants, and the cognitive and depression measures included.

Most of the longitudinal studies above measured depression as a unidimensional construct and did not distinguish between different symptom dimensions. However, late-life depression is a heterogeneous condition. Specific symptom presentations such as depressed affect, low positive affect, somatic and motivational, or cognitive symptoms may reflect distinct aetiologies, and may be differentially related to the nature and course of cognitive impairment. For instance, affective symptoms of depression may manifest as a psychological reaction to mild or transitory cognitive impairment, whereas an organic syndrome of depression, consisting of psychomotor and cognitive symptoms, may be more prevalent as cognitive functioning deteriorates and older adults lose insight about their cognitive deficits (Ritchie *et al.* 1999).

Previous reports suggest that motivational and somatic symptoms of depression may be more strongly related to cognitive impairment than affective symptoms. Cross-sectional findings suggest that ‘motivational disturbance’ was more strongly related to verbal fluency performance than ‘affective suffering’

symptoms (Castro-Costa *et al.* 2007; Brailean *et al.* 2015). Longitudinal findings suggest that patients with a history of vascular disease who had poorer baseline performance on executive function, processing speed and memory tasks showed a higher increase in a cluster of motivational and somatic symptoms of depression compared to mood symptoms over 7 years of follow-up (Kooistra *et al.* 2015). These findings are consistent with the depression-executive dysfunction hypothesis according to which motivational symptoms of depression tend to occur in the context of executive deficits, possibly due to vascular disease and a disruption of frontal-subcortical pathways (Alexopoulos *et al.* 1997, 2002). Evidence for the prominent role of motivational and somatic symptoms in persons with cognitive impairment comes also from studies suggesting that symptoms of fatigue, cognitive complaints and sleep disturbance were associated with ‘cognitive impairment no dementia’ in the absence of dysphoric and anhedonic symptoms (Potvin *et al.* 2010), and that motivational symptoms of depression were dominant in the preclinical phase of Alzheimer disease (Berger *et al.* 1999; Bartolini *et al.* 2005), and in mild cognitive impairment (Kumar *et al.* 2006). However, other findings suggest that depressed affect and somatic symptoms were similarly related to cognitive performance on attention and motor tasks in the general population (Baune *et al.* 2007).

Evidence on the association between positive affect and cognitive functioning is also inconclusive. Cross-sectional studies suggest that positive affect was a more robust predictor of cognitive performance across a variety of tasks than depressed affect, somatic symptoms or interpersonal difficulties (La Rue *et al.* 1995), that higher positive affect was related to better every day problem solving (Paterson *et al.* 2016), and that higher positive affect was related to better verbal fluency performance (before Bonferroni adjustment), but not better memory, speed or attention (Baune *et al.* 2007). Longitudinal findings by Turner *et al.* (2015) suggest that lower baseline levels of positive affect (but not somatic symptoms, interpersonal difficulties, or depressed affect scores) were associated with steeper decline in global cognition, episodic memory, and perceptual speed. Positive affect could help maintain cognitive function by reducing stress hormone levels and cardio-vascular risk, by improving health behaviours such as diet, sleep, and physical exercise, and by increasing the engagement in social interactions and cognitively stimulating activities (for a review see Pressman & Cohen, 2005).

Studies employing a longitudinal design and a multidimensional approach to depression are needed to clarify the direction of influence between depression symptom dimensions and cognitive functioning, and

to help gain a better understanding of the neurobiological and psychological mechanisms underlying the co-morbid manifestation of depression and cognitive impairment in late-life. Our study aims to examine longitudinal associations between specific depression symptom dimensions (i.e. depressed affect, positive affect, somatic symptoms) and specific domains of cognitive functioning (i.e. processing speed, inductive reasoning, immediate recall, delayed recall) in older adults. If depression symptoms develop as a psychological reaction to cognitive impairment, we would expect lower baseline cognitive functioning to predict an increase in depression symptoms over time. This effect may be stronger for affective symptoms of depression. If depression symptoms are a risk factor for cognitive impairment, we would expect higher initial depression levels to predict steeper cognitive decline. This effect may be stronger for somatic symptoms of depression. If cognitive impairment and depression symptoms share a similar aetiology (e.g. dementia-related neuropathology, cerebrovascular diseases) we would expect a synchronous relationship whereby an increase in depression symptoms would correlate with declining cognitive function over time. This effect is more likely to be observed for somatic symptoms of depression. The simultaneous examination of these hypotheses could help clarify the effect magnitude and direction of influence between cognitive abilities and late-life depression dimensions. For comparison purposes we include also an examination of the longitudinal associations between cognitive abilities and depression conceptualized as a unitary construct (i.e. total CES-D score).

Method

Participants

Data were used from the Longitudinal Aging Study Amsterdam (LASA; Huisman *et al.* 2011), an ongoing study exploring physical, emotional, cognitive and social functioning in late life in a nationally representative sample. Respondents were recruited from the population registers of 11 municipalities from three regions in The Netherlands, and were interviewed in their homes by trained persons. In the current study the baseline measurement consisted of data collected in 1995–1996 from participants aged 65–89 years ($N=1506$) with the aim of ensuring that the proportion of data present at baseline was over 90% on both depression and cognitive measures. Four follow-up measurements were included in this study: 1998–1999 (wave 2), 2001–2002 (wave 3), 2005–2006 (wave 4), and 2008–2009 (wave 5). Fig. 1 presents the number

of respondents included in each measurement wave, the attrition rates and the reasons for dropout.

Instruments

Depressive symptoms were assessed using the Centre for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977). Participants were asked to report how often they experienced certain symptoms of depression in the past week, and their responses were rated using a four-point Likert scale, where 0 = 'rarely or never'; 1 = 'some of the time'; 2 = 'occasionally'; 3 = 'mostly or always'. CES-D has good psychiatric properties in older adults (Himmelfarb & Murrell, 1983; Hertzog *et al.* 1990; McCallum *et al.* 1995). A cut-off score of 16 can be used to identify persons with major depression (Beekman *et al.* 1997). CES-D was originally posited as having a four-factor structure: depressed affect, positive affect, somatic symptoms and interpersonal difficulties (Radloff, 1977). This factor structure was confirmed in the LASA sample (Beekman *et al.* 1997; Brailean *et al.* 2016). However, the interpersonal difficulties factor may be poorly measured (i.e. it consists of only two items) and it is not in line with the current diagnosis criteria for depression (for a review see Carleton *et al.* 2013). Therefore, in our analyses we only included the subscale scores for positive affect (items: 4, 8, 12, 16), depressed affect (items: 3, 6, 9, 10, 14, 17, 18), and somatic symptoms (items: 1, 2, 5, 7, 11, 13, 20).

Episodic memory was assessed using the 15 Words Test, a Dutch version of the Auditory Verbal Learning Test (Rey, 1964). Fifteen words were verbally presented to participants and repeated over three trials. Participants were required to repeat the words they remembered at the end of each trial. The total score on the three trials was used as a measure of immediate recall. After a distraction period of about 20 min participants were asked to name again the words they remembered. This was used as a measure of delayed recall.

Information processing speed was assessed in LASA using an adaptation of the Coding Task (Savage, 1984). Participants were shown two rows, the upper one containing characters and the lower one being empty. Participants were asked to name the character in the bottom row which belonged to the character in the upper row and they were instructed to respond to the letter combinations as quickly and accurately as possible. The correct letter combination was presented at the top of the page. The task consisted of three trials and each trial lasted for 1 min. Scores were calculated based on the number of completed combinations. In our analyses we used the total score for the three trials. Because participants were asked to make a verbal response, it is considered that this

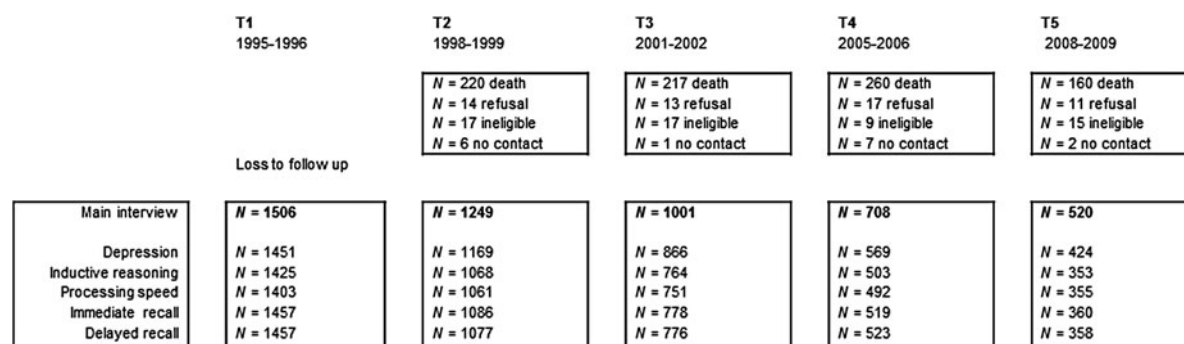


Fig. 1. Flow chart of the study sample.

adapted version of the task measures cognitive speed rather than motor speed.

Inductive reasoning was assessed using the Raven Coloured Progressive Matrices (RCPM; Raven, 1995). Participants were shown a drawing from which a section was missing and they were asked to identify the correct missing section from six alternatives patterns presented at the bottom of the page. Raven consists originally of three subsets: A, Ab and B, but only subsets A and B were used in LASA. Each subset consists of 12 items, and both items and subsets show a progressive increase in difficulty. The number of correct responses to each item was used to calculate the total score. The sum score of A and B subsets ranged from 0 to 24.

General cognitive performance was assessed with the Mini Mental State Examination (MMSE; Folstein et al. 1975), a widely used instrument in epidemiological studies to screen for cognitive impairment and to assess general cognitive functioning in older adults. The MMSE shows satisfactory reliability and construct validity (Tombaugh & McIntyre, 1992). Scores range from 0 to 30 with higher scores indicating better cognitive performance.

Statistical analysis

First, univariate latent growth curve models (LGCs), as a function of time in study, were fitted independently to each outcome measure: depressed affect, positive affect, somatic symptoms, immediate recall, delayed recall, processing speed and inductive reasoning. Univariate LGCs allow for an examination of (1) the initial level of a target outcome (i.e. intercept); (2) its rate of change (i.e. slope) and the form of this change (i.e. linear or nonlinear latent growth trajectory); (3) the association between the initial level of the outcome and its rate of change (e.g. persons who start off with poorer cognitive performance show steeper cognitive decline over time). Various predictors can also be added to these models to show their associations with the initial levels (i.e. intercept) and rate of

change (i.e. slope) in the target outcome. In our models the intercept of each target outcome was centred at baseline and a linear form of the latent growth trajectory was tested. Intercepts and slopes of all target outcomes were adjusted for baseline age (in years), gender and education (in years). Age and education were centred at their mean values in order to help with model estimation and with the interpretation of the estimates.

After establishing the linearity of the latent growth trajectories and ensuring good model fit in univariate LGCs, we conducted cross-domain LGCs to examine the association between each cognitive ability (inductive reasoning, processing speed, immediate recall or delayed recall) and each depression dimension (depressed affect, positive affect and somatic symptoms). On top of the parameters estimated in univariate LGCs, cross-domain LGCs estimated associations between: (1) baseline cognitive performance and baseline depression symptoms; (2) baseline cognitive performance and the rate of change in depression symptoms; (3) baseline depression symptoms and the rate of change in cognitive performance; (4) the rate of change in depression symptoms and the rate of change in cognitive performance (Fig. 2). These models were adjusted for baseline age (in years), gender and education (in years).

Sensitivity LGC analyses were conducted to investigate the association between depression and cognitive functioning in the context of adjustment for potential confounders. Based on previous research (Blazer, 2003; Alexopoulos, 2005; Alzheimer's Disease International, 2014; Baumgart et al. 2015; Vassilaki et al. 2015), the following confounders were considered as potentially relevant: chronic diseases (i.e. non-specific lung disease, cardiac disease, peripheral arterial disease, diabetes mellitus, cerebrovascular accident or stroke, osteoarthritis or rheumatoid arthritis, cancer, hypertension and a maximum of two other diseases of which symptoms and treatment persisted for at least 3 months), alcohol use (no, middle, and high

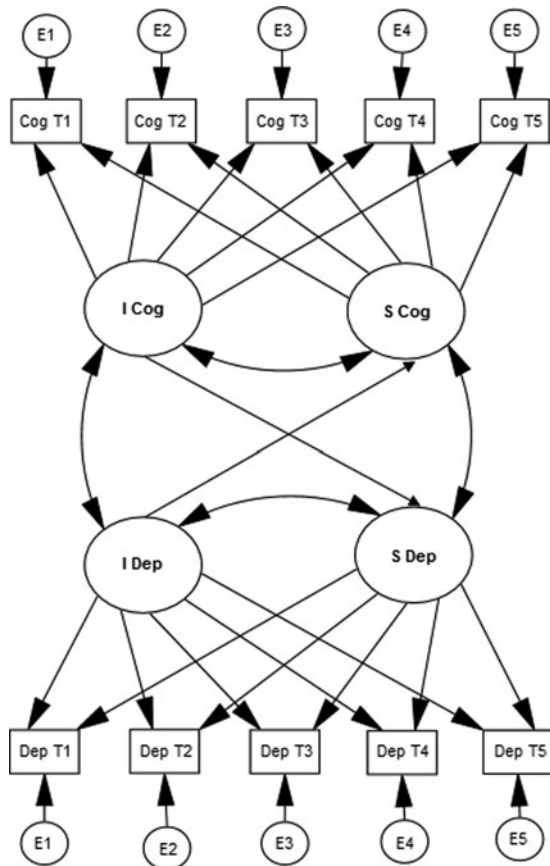


Fig. 2. Cross-domain latent growth curve model (LGCM). Cross-domain LGCM illustrating the association between depression and cognitive functioning. Single-headed arrows represent regression effects. Double-headed arrows represent correlations. The intercepts of both depression and cognition are centred at baseline. The slopes of cognition and depression represent changes in these outcomes over five assessment occasions during 13 years of follow-up. The intercepts and slopes of all depression dimensions and cognitive abilities were regressed on relevant covariates. For the sake of clarity, the effect of covariates on the intercept and slope of depression and cognition are not presented in this figure.

consumption according to the Netherlands Economic Institute index), exercise (total time spent on physical activities in minutes per day), social network (number of persons with whom the participant is has regular contact), use of antidepressant and anxiolytic medication (user *v.* non-user, based on an inspection of medicine bottles during the medical interview), smoking (current, past, or never smoker). We also repeated the cross-domain LGCM analyses using the total CES-D score instead of domain-specific scores. This additional set of sensitivity analyses included partially adjusted models (i.e. controlling for age, gender and education) and fully adjusted models (i.e. controlling for all the additional confounders mentioned above).

All analyses were conducted in MPlus v. 7.2 (Muthén and Muthén, 1998–2012). Maximum Likelihood Robust (MLR) estimation was used for all models. MLR is robust to non-normality and calculates parameters using both cases with complete data and cases with partially missing data. MLR estimation deals with missing data under the missing at random (MAR) assumption whereby attrition can be related to the observed values of both covariates and outcomes. When the missing data mechanism is MAR, missing data is assumed to be ‘non-informative’ or ‘ignorable’ (Little & Rubin, 1987) and model parameters estimated in the presence of missing data would be similar to the situation in which data had been complete. Model fit was evaluated based on the model χ^2 with a *p* value >0.05 indicating good model fit (Hu & Bentler, 1999); the comparative fit index (CFI) (Bentler, 1990) and the Tucker–Lewis index (TLI; Tucker & Lewis, 1973) with values >0.90 suggesting acceptable fit, and values >0.95 indicating good fit; the root mean square error of approximation (RMSEA) (Steiger, 1990) with values <0.06 indicating good fit.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Results

Descriptive statistics for our sample are presented in Table 1. Among respondents 51.7% were females, and 13.8% of participants had a MMSE score of ≤ 23 , indicative of cognitive impairment (Tombaugh & McIntyre, 1992). A CES-D score of ≥ 16 , indicative of clinically relevant depressive symptoms, was found in 15.8% ($N=228$) of participants (Berkman *et al.* 1986; Beekman *et al.* 1997). Clinical interviews using the Diagnostic Interview Schedule (Robins *et al.* 1981) were carried out among participants with a CES-D score of ≥ 16 . Among those interviewed, 37 had a diagnosis of depression in the past 6 months; 21 of them experienced their first episode of depression before age 60 years, and 16 of them experienced their first episode of depression after age 60 years. The age of depression onset was based on participants’ self-reports. The use of antidepressants and anxiolytics was related to cognitive performance on some, but not all cognitive tests (see Supplementary Table S2).

Attrition rates and the reason for dropout are presented in Fig. 1. The high attrition rates observed in our study are a typical finding in longitudinal ageing

Table 1. Descriptive statistics

Continuous measures	N	Mean	S.D.	Categorical measures	Category	N	%
Age (years)	1506	75.9	6.6	Gender	Male	725	48
Education (years)	1504	8.9	3.3		Female	778	52
Depressed affect	1451	1.8	2.9	Chronic diseases	0	237	16
Positive affect	1408	8.6	3.1		1	454	30
Somatic symptoms	1443	2.9	3.1		2	429	29
Processing speed	1403	68.1	22.0		3	232	15
Inductive reasoning	1425	17.2	4.1		4	112	7
Immediate recall	1457	18.8	6.4		≥ 5	38	3
Delayed recall	1457	5.5	3.0	Antidepressants	User	41	3
MMSE	1502	26.5	3.3		Not user	1462	97
Physical activity	1438	40	57	Anxiolytics	User	103	7
Social network size	1447	14.0	8.2		Not user	1400	93
				Smoking	Never	539	36
					Past	680	45
					Current	288	19
				Alcohol	Never	388	26
					Moderate	975	65
					Severe	140	9

MMSE, Mini Mental State Examination.

Physical activity was measured as the total time spent being physically active in minutes per day; social network was measured as the number of persons with whom the participant has regular contact.

studies. Mortality accounted for over 80% of dropout rates. Other reasons included refusal, ineligibility and lack of contact. Higher dropout rates over the 13 years of follow-up were associated with being older [odds ratio (OR) 1.19, 95% confidence interval (CI) 1.16–1.21], being male (OR 0.56, 95% CI 0.45–0.70), having lower baseline levels of immediate recall (OR 0.88, 95% CI 0.86–0.90), delayed recall (OR 0.78, 95% CI 0.75–0.81), processing speed (OR 0.97, 95% CI 0.97–0.98), and inductive reasoning (OR 0.85, 95% CI 0.83–0.88), as well as having higher baseline levels of depressed affect (OR 1.07, 95% CI 1.03–1.11) and somatic symptoms (OR 1.05, 95% CI 1.01–1.09), and lower levels of positive affect (OR 0.95, 95% CI 0.91–0.98).

Univariate latent growth models

Table 2 presents results from univariate models adjusted for age, gender and education. Model fit for all univariate models was good and it ranged from CFI=0.94, TLI=0.92, RMSEA=0.07 (90% CI 0.06–0.08) for immediate recall to CFI=1.00, TLI=1.00, RMSEA<0.01 (90% CI 0.00–0.02) for inductive reasoning. The mean of the intercept and slope was statistically significant for all outcome measures, indicating a significant linear change in scores over time. Sample and estimated means for each depression and cognitive outcome measure are presented in Supplementary Table S4. Supplementary Figs S1–S7

present the observed individual scores for each cognitive domain and each depression dimension across time points. Participants showed an increase in depressed affect and somatic symptoms, as well as a drop in positive affect over time. A decline in performance was observed for all cognitive abilities. The intercept and slope of our outcome measures should be interpreted as the initial level and rate of change in the outcome for a person of average age (75.9 years) and average level of education (8.9 years). The variance of the slope for positive affect was not statistically significant, whereas the variance of the intercept and slope for all other outcome measures was statistically significant, indicating that both the initial level and rate of change in depression and cognitive scores varied between individuals. The only significant correlation between intercept and slope was found for processing speed, indicating that participants with higher baseline performance had steeper decline in processing speed over time, which could reflect an effect of regression to the mean. The rate of decline in other cognitive measures was not dependent on the initial level of cognitive performance.

Cross-domain latent growth models

Table 3 shows results of the cross-domain models. All cross domain models fitted the data well: CFI ≥ 0.95; TLI ≥ 0.94; RMSEA ≤ 0.04 (90% CI 0.04–0.05). Fit

Table 2. Estimates for univariate latent growth curve models (LGCMs)

Measure	Mean intercept	Mean slope	Variance intercept	Variance slope	Correlation between intercept and slope	
					<i>r</i>	S.E.
Inductive reasoning	17.06	−0.17	7.22	0.02	0.06	0.13
Processing speed	65.60	−1.47	278.4	0.67	−0.22***	0.06
Immediate recall	17.17	−0.42	18.75	0.05	−0.07	0.13
Delayed recall	4.68	−0.18	4.58	0.02	−0.15	0.09
Depressed affect	1.22	0.09	3.96	0.01	−0.08	0.19
Positive affect	9.07	−0.13	4.00	<0.01	−0.01	0.26
Somatic symptoms	2.38	0.15	5.10	0.02	−0.12	0.15

*** $p < 0.001$; the value of the slope reflects the yearly change in the outcome measure; means and variances of all intercepts and slopes are statistically significant, except for the variance of the slope for positive affect; results presented are based on univariate LGCMs for each outcome measure, after adjustment for age, gender and education.

indices for each model are presented in Supplementary Table S3. Lower baseline levels of processing speed and immediate recall were significantly associated with higher baseline levels of depressed affect and somatic symptoms, as well as lower levels of positive affect. Higher baseline levels of inductive reasoning were significantly associated with lower depressed affect and lower somatic symptoms. No association was found between baseline levels of delayed recall and baseline levels of depressed affect, positive affect or somatic symptoms. Baseline delayed recall performance predicted a statistically significant steeper increase in depressed affect over time. Initial levels of performance in other cognitive domains were unrelated to rates of change in depressed affect, positive affect or somatic symptoms. Also, initial levels of depressed affect, positive affect or somatic symptoms were unrelated to changes over time in any cognitive domains. In terms of the association between changes in depressive symptoms and changes in cognitive functioning over time, we only found that decline in processing speed performance was related to an increase in somatic symptoms over time.

Sensitivity analyses revealed that adjustment for additional confounders (i.e. number of chronic diseases, physical activity, social network size, alcohol use, use of antidepressant and anxiolytic medication, and smoking) did not change substantive conclusions about the longitudinal associations between depression symptom-dimensions and cognitive abilities (see Supplementary Table S1). The association between processing speed decline and the increase in somatic symptoms remained statistically significant in the fully adjusted models, whereas the effect of baseline delayed recall scores on changes in depressed affect was marginally significant ($p = 0.05$). An additional

set of sensitivity analyses using the total CES-D scores revealed that overall depression levels at baseline did not predict the rate of decline in any cognitive ability (see Supplementary Table S5). Higher initial levels of delayed recall predicted an increase in overall depression levels over time, and the effect remained statistically significant in the fully adjusted model. An increase in overall depression levels was associated with decline in immediate recall, processing speed and inductive reasoning in the partially adjusted models, but only the association between processing speed and depression symptoms remained statistically significant in the fully adjusted models.

Conclusions

Using data from a large nationally representative sample of LASA and a multidimensional approach to late-life depression, this longitudinal study examined associations between depression dimensions and cognitive functioning in late-life. Our findings suggest significant cross-sectional associations between baseline depression dimensions and cognitive performance on processing speed, inductive reasoning and immediate recall tasks. These findings are consistent with evidence that late-life depression co-occurs with impairment in fluid cognitive abilities (e.g. Comijs *et al.* 2001; Butters *et al.* 2004; Sheline *et al.* 2006; Baune *et al.* 2007; Koenig *et al.* 2014). Our longitudinal findings suggest that older adults showed significant decline over time in all cognitive abilities, which is in line with a large body of knowledge suggesting that cognitive decline is part of normal ageing (e.g. Brayne *et al.* 1999; Wilson *et al.* 1999; Park *et al.* 2003). Furthermore, older adults showed an increase in depressed affect and somatic symptoms, as well as a

Table 3. Estimates for cross-domain latent growth curve models

	Depression dimension					
	Depressed affect		Positive affect		Somatic symptoms	
	β	S.E.	β	S.E.	β	S.E.
Cognitive ability						
Processing speed						
I Cog \leftrightarrow I Dep	−0.16***	0.03	0.13**	0.04	−0.20***	0.04
I Dep \rightarrow S Cog	0.08	0.08	−0.13	0.08	0.14	0.07
I Cog \rightarrow S Dep	−0.18	0.10	0.28	0.21	−0.04	0.10
S Cog \leftrightarrow S Dep	−0.18	0.12	0.82	0.53	−0.38*	0.16
Inductive reasoning						
I Cog \leftrightarrow I Dep	−0.14**	0.05	0.07	0.05	−0.18***	0.05
I Dep \rightarrow S Cog	−0.04	0.11	0.08	0.11	0.01	0.11
I Cog \rightarrow S Dep	−0.12	0.12	0.29	0.26	0.12	0.12
S Cog \leftrightarrow S Dep	−0.26	0.17	0.64	0.51	−0.32	0.18
Immediate recall						
I Cog \leftrightarrow I Dep	−0.11**	0.04	0.10*	0.05	−0.12**	0.04
I Dep \rightarrow S Cog	0.16	0.11	−0.06	0.11	0.11	0.10
I Cog \rightarrow S Dep	−0.18	0.12	0.10	0.21	−0.19	0.12
S Cog \leftrightarrow S Dep	−0.32	0.17	0.56	0.43	−0.25	0.17
Delayed recall						
I Cog \leftrightarrow I Dep	−0.07	0.04	0.04	0.04	−0.08	0.04
I Dep \rightarrow S Cog	−0.02	0.10	0.04	0.10	0.01	0.10
I Cog \rightarrow S Dep	−0.25*	0.11	0.45	0.28	−0.18	0.11
S Cog \leftrightarrow S Dep	0.06	0.14	−0.21	0.35	−0.03	0.14

β , Standardized estimates; I Cog, intercept of cognitive ability; I Dep, intercept of depression dimension; S Cog, slope of cognitive ability; S Dep, slope of depression dimension; double-headed arrows represent correlations, whereas single-headed arrows represent regression effects; all models are adjusted for age, gender and education.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, statistically significant results are presented in bold.

drop in positive affect over time, which is consistent with previous findings suggesting an increase in depressive symptoms in old age (Meeks *et al.* 2011; Sutin *et al.* 2013).

Regarding the effect of baseline cognitive performance on the course of depression symptom-dimensions, our findings indicate that poor delayed recall performance at baseline predicted an increase in depressed affect over time, but it did not predict changes in positive affect or somatic symptoms of depression. Poorer delayed recall performance at baseline predicted also an increase in overall depression symptoms (i.e. total CES-D score), which is consistent with previous reports (Vinkers *et al.* 2004; Jajodia & Borders, 2011). The increase in depressed affect in persons with poor baseline delayed recall may indicate a psychological reaction to perceived memory dysfunction. Older adults may be more likely to notice their memory problems than other cognitive dysfunction (such as slow processing speed). Memory failure may cause difficulties in daily living and related-challenges, which could lead to increasing depressed affect. As our study did not assess subjective memory complaints, the level of

insight that participants had about their memory loss remains unknown. However, the effect of initial delayed recall performance on the slope of depressed affect remained statistically significant after adjusting for relevant confounders. An alternative explanation for our finding is that the same neurodegenerative mechanisms may underlie both delayed recall dysfunction and the increase in depression symptoms. According to previous reports, delayed recall measures predict conversion from mild cognitive impairment to Alzheimer's disease better than measures of other cognitive abilities (Gainotti *et al.* 2014), and the risk of conversion is higher among older adults with amnesic cognitive impairment who also present clinical depression, compared to those without depression (Modrego & Ferrandez, 2004). If delayed recall dysfunction and depression symptoms were manifestations of dementia-related neurodegenerative processes, we would have expected delayed recall decline to correlate with an increasing trajectory of depression symptoms. This effect was not found in our study.

Regarding the effect of baseline depression symptom-dimensions on cognitive decline, our findings

suggest that baseline levels of depressed affect, positive affect, and somatic symptoms did not predict the rate of cognitive decline. This was also the case for overall depression symptoms (total CES-D score). These findings argue against the hypothesis that depression may be a risk factor for cognitive decline. Our findings conflict with previous reports indicating that higher baseline depression scores predicted accelerated decline in episodic memory (Panza *et al.* 2009; Zahodne *et al.* 2014), processing speed (van den Kommer *et al.* 2013), and general cognitive performance (Gale *et al.* 2012; van den Kommer *et al.* 2013), and are inconsistent with meta-analytic evidence that depressed persons have an increased risk of incident dementia (Ownby *et al.* 2006; Diniz *et al.* 2013; Alzheimer's Disease International, 2014; Cherbuin *et al.* 2015). It is possible that a prospective effect of depression on cognitive decline may have been observed with a shorter follow-up duration than the one used in our study. According to previous reports (Alzheimer's Disease International, 2014; Mirza *et al.* 2014), the prospective effect of depression symptoms on dementia was stronger in studies with shorter follow-up durations, which is consistent with the hypothesis that depression may be a prodromal manifestation of dementia rather than an independent risk factor. Furthermore, it is possible that a clinical diagnosis of depression, rather than subclinical depression symptoms, may flag an increased risk for cognitive decline. In our study only a small percentage of participants had clinically significant depression symptoms (i.e. a CES-D score of ≥ 16) or a clinical diagnosis of depression.

Regarding the associations between changes in specific symptom-dimensions of depression and changes in cognitive functioning, our findings suggest that increasing severity of somatic symptoms of depression over 13 years of follow-up showed a specific association with steeper decline in processing speed. This effect remained statistically significant after adjusting for potential confounders. After adjustment for confounders, an increase in overall depression symptoms (i.e. total CES-D score) was only associated with declining processing speed over time. This is inconsistent with previous reports suggesting that changes in processing speed were unrelated to changes in overall depression symptoms in participants aged ≥ 55 years (van den Kommer *et al.* 2013). The discrepancy between these findings may be partly explained by the inclusion of older participants in our study (aged ≥ 65 years). The concurrent manifestation of somatic symptoms of depression and slow processing speed may be more relevant at advanced ages, but the underlying aetiological mechanisms are yet to be clarified. Previously, Kooistra *et al.* (2015) reported

that slower processing speed at baseline was associated with a larger increase in a cluster of somatic and motivational symptoms of depression (compared to mood symptoms) over 7 years of follow-up. The somatic and motivational symptoms of depression assessed by Kooistra *et al.* (2015) were similar to the symptoms assessed in our study with the somatic subscale of CES-D (i.e. appetite disturbance, energy loss, sleep disturbance, concentration problems, psychomotor retardation). Taken together, these findings suggest that somatic and motivational symptoms of depression and processing speed impairment may be clinical manifestation of the same neurodegenerative processes, such as white matter lesions or vascular disease (Alexopoulos *et al.* 1997, 2002; Naarding *et al.* 2005). The specific association between changes in somatic symptoms and changes in processing speed in our study may also reflect the fact that the somatic subscale of CES-D and the processing speed task used in our study measure similar constructs. For instance, some of the items that are part of the somatic subscale of CES-D assess cognitive complaints (i.e. concentration difficulties, feeling that everything is an effort, not being able to get going).

Our findings suggest that an accelerated rate of cognitive decline may be associated with an increase in depression symptoms over time rather than with higher initial depression scores. In particular, the presence of somatic symptoms of depression may indicate a chronic course of cognitive decline which is primarily reflected in slow processing speed. These findings are consistent with evidence that the risk of dementia is particularly high in older adults who experience a chronic course of depression (i.e. an increasing trajectory of depression), but not in those who experience transient depression (i.e. high scores at a particular time point, followed by remission) (Kaup *et al.* 2016; Mirza *et al.* 2016).

Strengths of this study include the large sample size, the long follow-up period, the dimensional approach to late-life depression, and the assessment of several cognitive abilities which are commonly impaired in late-life depression. A first notable limitation of our study is the high attrition rate over the course of the follow-up, largely due to mortality. Participants with more severe depression symptoms and poorer cognitive functioning at baseline were more likely to drop out from the study over the course of the follow-up. The selective loss of more cognitively impaired and more severely depressed individuals over the course of the follow-up may have resulted in an underestimation of the effects found in this study. We dealt with missing data using the maximum likelihood estimation under the missing at random assumption. However, this assumption cannot be verified, and there remains

a possibility that findings may differ if data were missing not at random. Second, our findings are only relevant to community dwelling older adults and cannot be generalized to clinical populations. Third, it is possible that our findings may relate to the specific tasks used rather than the cognitive domains being studied. However, we cannot examine this given that only one test was available for each cognitive measure in LASA. Fourth, our models are not adjusted for multiple testing. Although Type 1 error (i.e. the probability of detecting an effect that is not present) could have been reduced by adjusting for multiple testing, this would have been at the expense of the Type 2 error (i.e. failing to detect an effect that is present), and would have reduced the power to detect potentially important effects (Gelman *et al.* 2012). Due to the large number of tests conducted and the correlations among model parameters, traditional methods of correcting for Type 1 error may be overly conservative in the context of our LGCM analyses. Of note, the simultaneous estimation of the effect of baseline depression on cognitive decline and the effect of baseline cognitive performance on the course of depressive symptoms allows to determine relative predictive associations, without implying a true causal effect and without clarifying the aetiological factors that may underlie the observed associations.

In conclusion, our findings do not support the hypothesis that specific depression symptom clusters may predict an increased rate of cognitive decline. However, our findings support a prospective effect of memory function on the course of depressed affect, which may indicate a psychological reaction to poor memory function. This implies that maintaining good cognitive functioning by engaging in memory enhancing activities could help older adults cope with ageing related challenges and protect them against depression. Furthermore, our findings support a synchronous longitudinal association between the course of processing speed performance and the course of somatic symptoms of depression. More research is needed to understand whether somatic symptoms of depression are an early sign of cognitive impairment or a prodromal syndrome of dementia, and whether the early diagnosis and treatment of depression among older adults presenting somatic complaints may improve cognitive outcomes. Future studies could also examine whether older adults with specific trajectory classes (e.g. chronic, remitting, relapsing depression) of depression symptom-dimensions (e.g. depressed affect, positive affect, somatic symptoms) present an accelerated rate of cognitive decline and an increased risk of dementia. A better understanding of the nature, direction and timing of the association between depression symptom dimensions and cognitive

functioning in late-life, and of the underlying aetiological mechanisms, could help develop targeted interventions aimed at improving cognitive outcomes among older adults with specific depression symptom profiles.

Supplementary material

The supplementary material for this article can be found at <https://doi.org/10.1017/S003329171600297X>.

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Declaration of Interest

None.

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6.1 SUPPLEMENTARY MATERIALS CHAPTER 6

These supplementary materials were presented in the following journal publication:

Brailean, A., Aartsen, M. J., Muniz-Terrera, G., Prince, M., Prina, A. M., Comijs, H. C., . . .
Beekman, A. (2016). Longitudinal associations between late-life depression
dimensions and cognitive functioning: a cross-domain latent growth curve analysis.
Psychological Medicine, 1-13. doi:10.1017/S003329171600297X

LGCM model - syntax example

Data:

File is C:/Users/Anamaria/Desktop/LGCM paper/LGGM model 1.dat;

Variable:

Names are respnr sex aedu cage Ccode Dcode Ecode Fcode Gcode
CSom DSom ESom FSom GSom;

Missing are . ;

Usevariables are Ccode Dcode Ecode Fcode Gcode
CSom DSom ESom FSom GSom sex age edu;

Define:

age = cage - 75.88;

edu = aedu - 8.87;

ANALYSIS:

ESTIMATOR IS MLR;

COVERAGE = 0.10;

Model:

icode scode | Ccode@0 Dcode@3 Ecode@6 Fcode@10 Gcode@13;

iSom sSom | CSom@0 DSom@3 ESom@6 FSom@10 GSom@13;

sSom on icode;

scode on iSom;

iSom with icode;

sSom with scode;

iSom with sSom;

icode with scode;

iSom sSom on sex age edu;

icode scode on sex age edu;

OUTPUT: SAMPSTAT RESIDUAL STANDARDIZED Modindices(All 10)
CINTERVAL PATTERNS TECH3 TECH4 TECH1 ;

Supplementary Table S1. Estimates for Cross-Domain Latent Growth Curve Models adjusted for confounders

Cognitive ability	Depression dimension					
	Depressed affect		Positive affect		Somatic symptoms	
Processing speed	β	S.E.	β	S.E.	β	S.E.
I Cog \longleftrightarrow I Dep	-0.11**	0.03	0.06	0.04	-0.16***	0.04
I Dep \rightarrow S Cog	0.07	0.08	-0.14	0.08	0.14	0.07
I Cog \rightarrow S Dep	-0.18	0.10	0.31	0.23	-0.04	0.10
S Cog \longleftrightarrow S Dep	-0.17	0.13	0.97	0.76	-0.41*	0.17
Inductive reasoning						
I Cog \longleftrightarrow I Dep	-0.11*	0.05	0.07	0.05	-0.16**	0.05
I Dep \rightarrow S Cog	-0.04	0.12	0.08	0.11	0.04	0.12
I Cog \rightarrow S Dep	-0.14	0.12	0.29	0.26	0.10	0.13
S Cog \longleftrightarrow S Dep	-0.17	0.17	0.64	0.51	-0.27	0.19
Immediate recall						
I Cog \longleftrightarrow I Dep	-0.07	0.04	0.04	0.05	-0.08	0.04
I Dep \rightarrow S Cog	0.16	0.11	-0.01	0.12	0.10	0.11
I Cog \rightarrow S Dep	-0.16	0.12	0.02	0.24	-0.21	0.13
S Cog \longleftrightarrow S Dep	-0.30	0.17	0.83	1.06	-0.22	0.18
Delayed recall						
I Cog \longleftrightarrow I Dep	-0.03	0.04	-0.01	0.05	-0.05	0.04
I Dep \rightarrow S Cog	-0.01	0.11	0.05	0.11	0.03	0.11
I Cog \rightarrow S Dep	-0.21	0.11	0.42	0.32	-0.17	0.12
S Cog \longleftrightarrow S Dep	0.02	0.15	-0.25	0.69	-0.05	0.15

Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; β = standardized estimates; Double headed arrows represent correlations, whereas single headed arrows represent regression effects; All models are adjusted for the number of chronic diseases, physical activity, social network size, use of antidepressant and anxiolytic medication, alcohol use, and smoking; I Cog = intercept of cognitive ability; I Dep = intercept of depression dimension; S Cog = slope of cognitive ability; S Dep = slope of depression dimension.

Supplementary Table S2. Differences in baseline cognitive performance according to medication status

	Use of antidepressants			Use of anxiolytics		
	Yes (N=41)	No (N=1462)		Yes (N=103)	No (N=1400)	
	Means		B	Means		B
Immediate recall	16.5	18.8	-2. 25*	17.2	18.8	-1.61*
Delayed recall	4.5	5.5	-1.03*	4.7	5.5	-0.81*
Processing speed	63.3	68.2	-4.93	62.0	68.5	-6.51**
Inductive reasoning	16.6	17.2	-0.59	15.7	17.3	-1.54***
MMSE	25.9	26.5	-0.61	25.9	26.5	-0.61

Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Supplementary Table S3. Model fit for unadjusted and partially adjusted models

	Depressed affect				Positive affect				Somatic symptoms			
	chi ² (df)	CFI	TLI	RMSEA (90 % CI)	chi ² (df)	CFI	TLI	RMSEA (90 % CI)	chi ² (df)	CFI	TLI	RMSEA (90 % CI)
Processing speed												
Unadjusted	81 (41)	0.99	0.99	0.03 (0.02–0.03)	97 (41)	0.99	0.98	0.03 (0.02–0.04)	106 (41)	0.98	0.98	0.03 (0.02–0.04)
Partially adjusted	112 (59)	0.99	0.99	0.02 (0.01–0.03)	121 (59)	0.99	0.98	0.03 (0.02–0.03)	131 (59)	0.99	0.98	0.03 (0.02–0.03)
Inductive reasoning												
Unadjusted	42 (41)	1.00	1.00	0.01 (0–0.02)	54 (41)	0.99	0.9	0.02 (0–0.03)	67 (41)	0.99	0.99	0.02 (0.01–0.03)
Partially adjusted	56 (59)	1.00	1.00	<0.01 (0–0.01)	61 (59)	1.00	1.00	0.01 (0–0.02)	74 (59)	0.99	0.99	0.01 (0–0.02)
Immediate recall												
Unadjusted	149 (41)	0.95	0.95	0.04 (0.04–0.05)	194 (41)	0.94	0.93	0.05 (0.04–0.06)	192 (41)	0.94	0.94	0.05 (0.04–0.06)
Partially adjusted	175 (59)	0.96	0.95	0.04 (0.03–0.04)	207 (59)	0.95	0.94	0.04 (0.03–0.05)	211 (59)	0.96	0.94	0.04 (0.04–0.05)
Delayed recall												
Unadjusted	167 (41)	0.95	0.94	0.05 (0.04–0.05)	194 (41)	0.94	0.93	0.05 (0.04–0.06)	191 (41)	0.95	0.94	0.05 (0.04–0.06)
Partially adjusted	191 (59)	0.96	0.95	0.04 (0.03–0.05)	203 (59)	0.96	0.94	0.04 (0.03–0.05)	205 (59)	0.96	0.95	0.04 (0.03–0.05)

Note: Unadjusted models do not include any covariates; partially adjusted models include the effects of age, gender and education on cognitive abilities and depression dimensions; this table does not include model fit information for the fully adjusted models (i.e., controlling for age, gender, education, number of chronic diseases, physical activity, social network size, use of antidepressant and anxiolytic medication, alcohol use, and smoking). However, all fully adjusted models fitted the data well and the fit values were similar to the ones in the partially adjusted models.

Supplementary Table S4. Sample and estimated means for each outcome measure

	Time				
	1	2	3	4	5
Sample means					
Depressed affect	1.8	2.0	2.4	2.5	2.5
Positive affect	8.6	8.2	7.6	7.4	7.8
Somatic symptoms	2.9	3.5	3.8	4.1	4.3
Immediate recall	18.7	17.0	17.1	14.2	12.4
Delayed recall	5.5	4.7	4.8	3.5	2.6
Inductive reasoning	17.2	16.5	16.2	15.5	15.0
Processing speed	67.9	64.8	60.8	54.8	47.8
Model estimated means					
Depressed affect	1.9	2.0	2.2	2.5	2.7
Positive affect	8.5	8.2	7.9	7.5	7.2
Somatic symptoms	3.0	3.3	3.7	4.2	4.5
Immediate recall	18.8	17.4	16.1	14.3	13.0
Delayed recall	5.5	4.9	4.3	3.5	2.8
Inductive reasoning	17.2	16.7	16.2	15.5	15.0
Processing speed	68.4	64.4	60.3	54.9	50.8

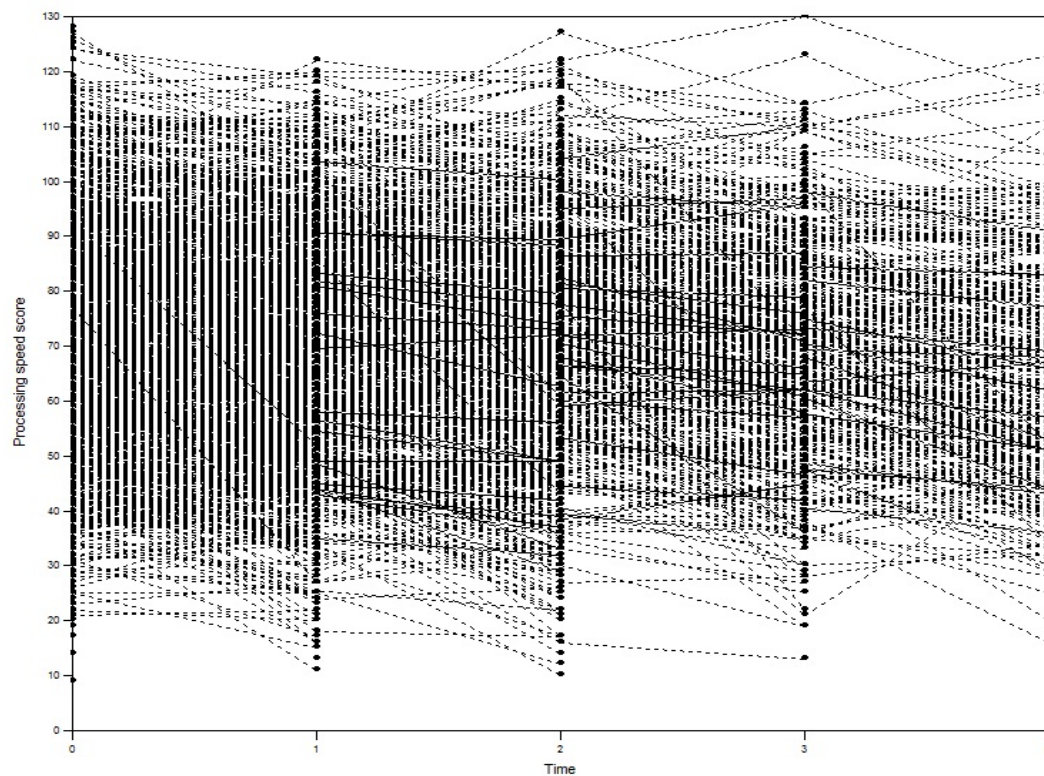
Note: Presented means are based on models adjusted for age, gender and education

Supplementary Table S5. LGCM estimates of the associations between overall depression scores and cognitive abilities

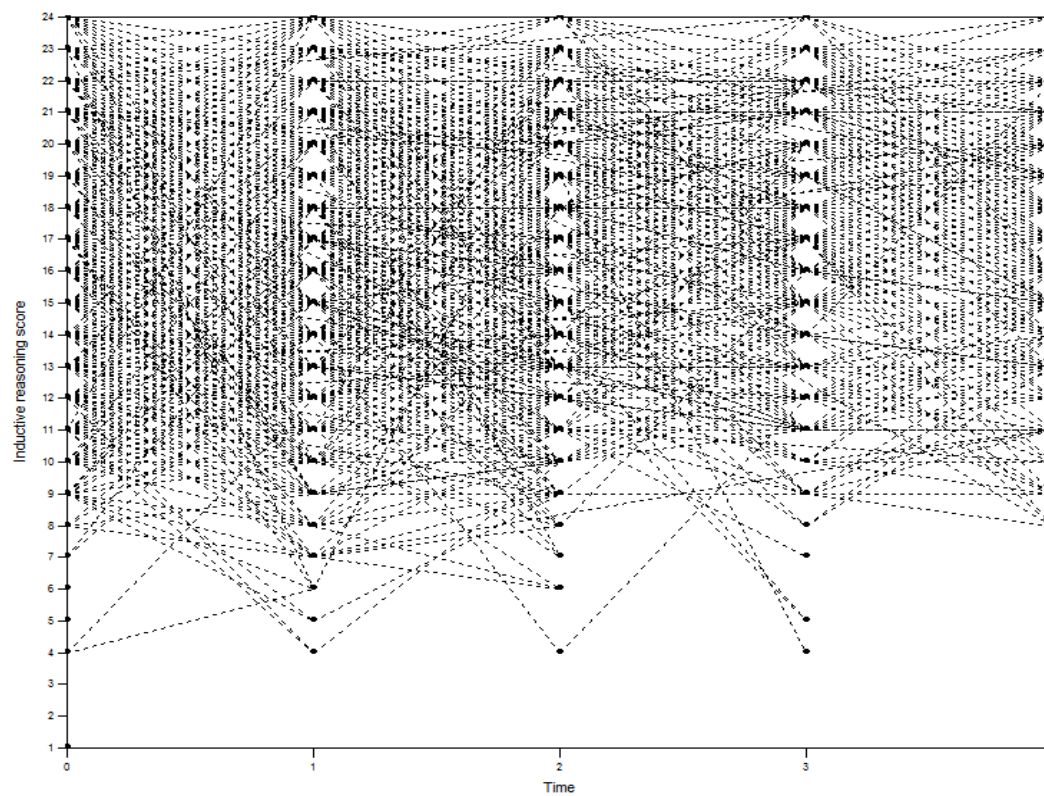
Cognitive ability	Overall depression scores			
	Partially adjusted models		Fully adjusted models	
	β	S.E.	β	S.E.
Processing speed				
I Cog \longleftrightarrow I Dep	-0.19***	0.03	-0.13***	0.03
I Dep \longrightarrow S Cog	0.13	0.08	0.13	0.08
I Cog \longrightarrow S Dep	-0.15	0.10	-0.14	0.10
S Cog \longleftrightarrow S Dep	-0.40**	0.14	-0.43**	0.14
Inductive reasoning				
I Cog \longleftrightarrow I Dep	-0.15***	0.04	-0.12**	0.05
I Dep \longrightarrow S Cog	-0.05	0.11	-0.04	0.12
I Cog \longrightarrow S Dep	-0.09	0.12	-0.09	0.12
S Cog \longleftrightarrow S Dep	-0.33*	0.16	-0.28	0.16
Immediate recall				
I Cog \longleftrightarrow I Dep	-0.12**	0.04	-0.07	0.04
I Dep \longrightarrow S Cog	0.11	0.10	0.08	0.11
I Cog \longrightarrow S Dep	-0.19	0.12	-0.17	0.12
S Cog \longleftrightarrow S Dep	-0.32*	0.16	-0.31	0.16
Delayed recall				
I Cog \longleftrightarrow I Dep	-0.07	0.04	-0.02	0.04
I Dep \longrightarrow S Cog	-0.02	0.10	-0.01	0.10
I Cog \longrightarrow S Dep	-0.28*	0.11	-0.24*	0.11
S Cog \longleftrightarrow S Dep	0.05	0.14	0.01	0.14

Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; β = standardized estimates; statistically significant results are presented in bold; double headed arrows represent correlations, whereas single headed arrows represent regression effects; I Cog = intercept of cognitive ability; I Dep = intercept of depression symptoms; S Cog = slope of cognitive ability; S Dep = slope of depression symptoms. Partially adjusted models control only for age, gender and education. Fully adjusted models additionally control for number of chronic diseases, physical activity, social network size, use of antidepressant and anxiolytic medication, alcohol use, and smoking;

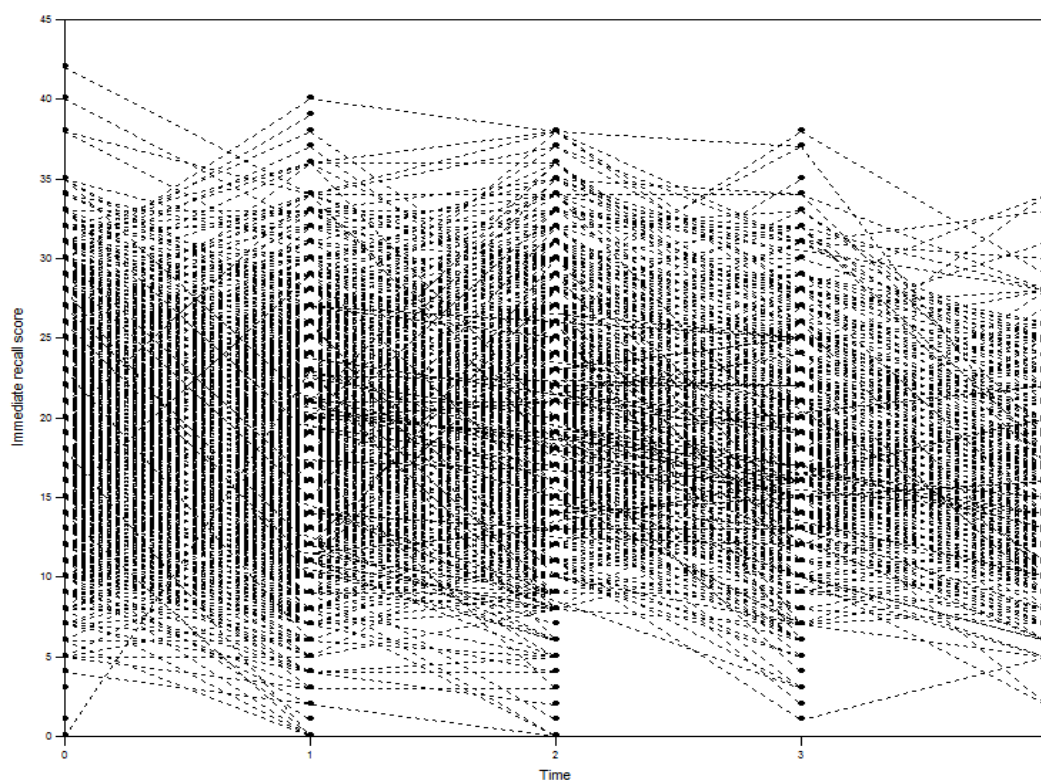
Supplementary Figure S1. Individual trajectories of processing speed



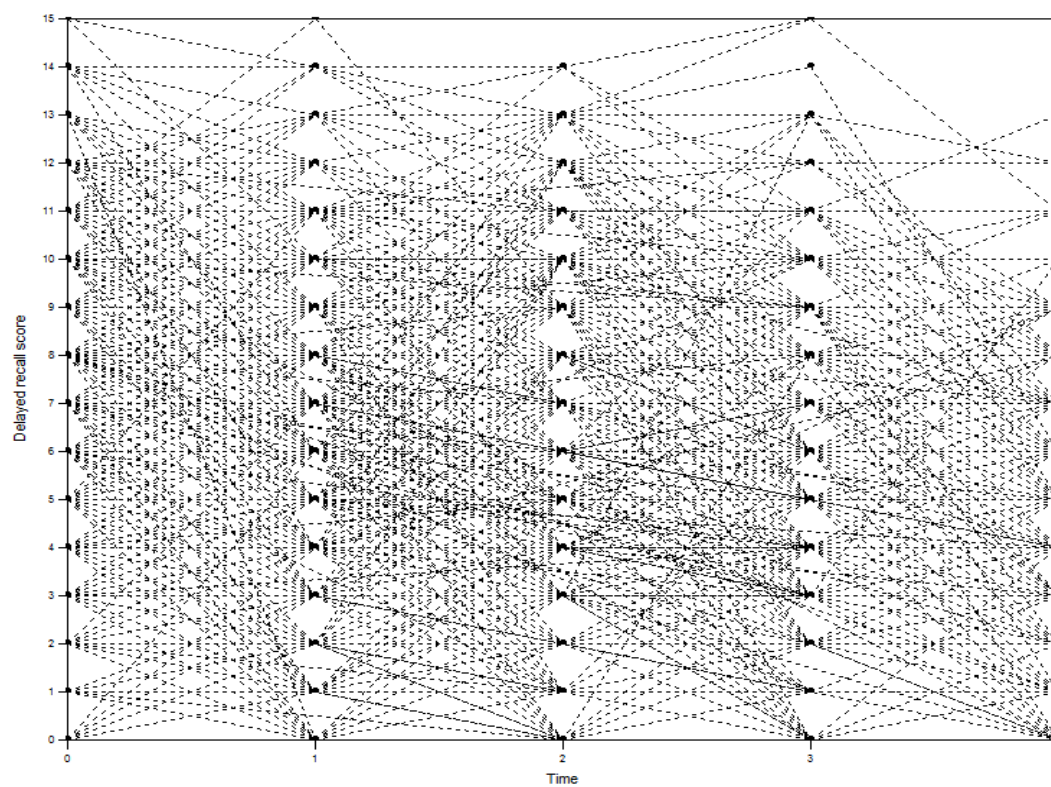
Supplementary Figure S2. Individual trajectories of inductive reasoning



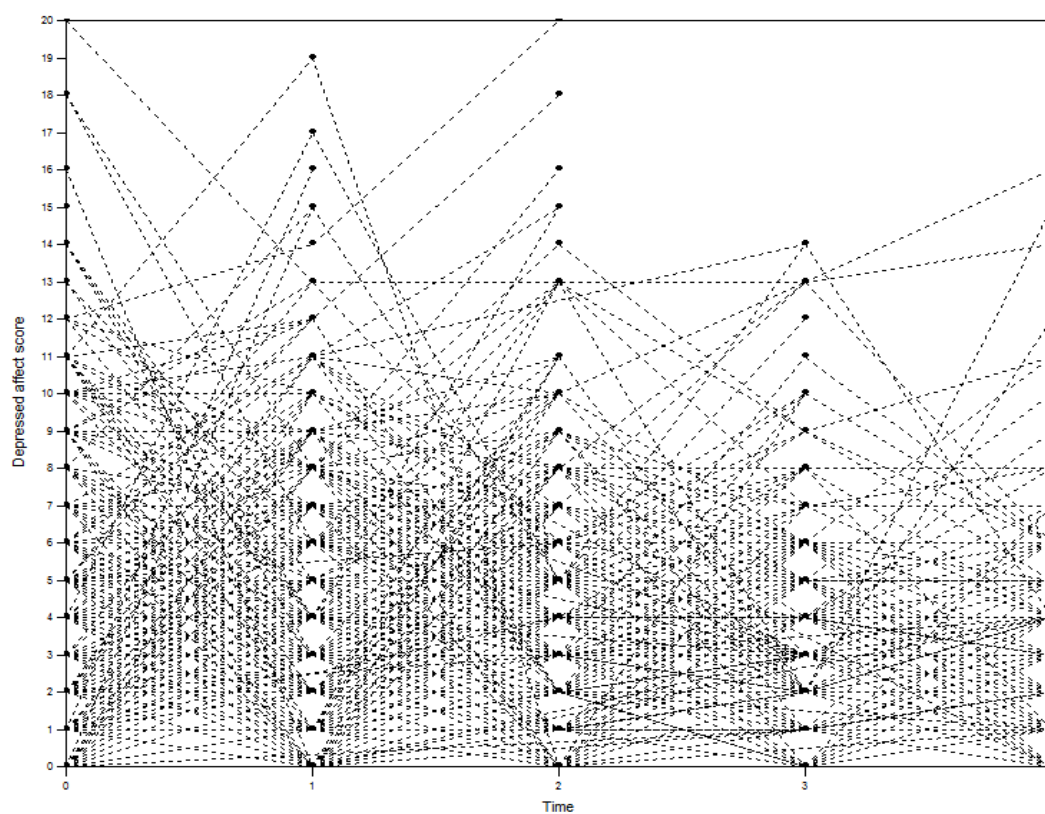
Supplementary Figure S3. Individual trajectories of immediate recall



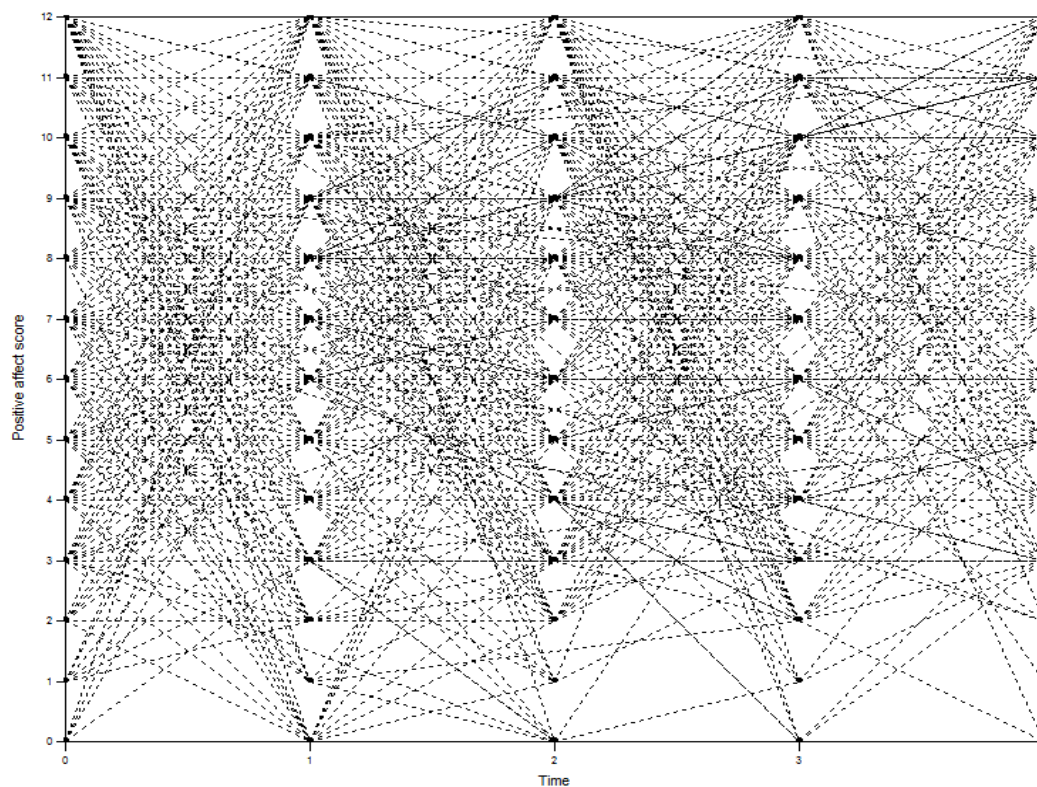
Supplementary Figure S4. Individual trajectories of delayed recall



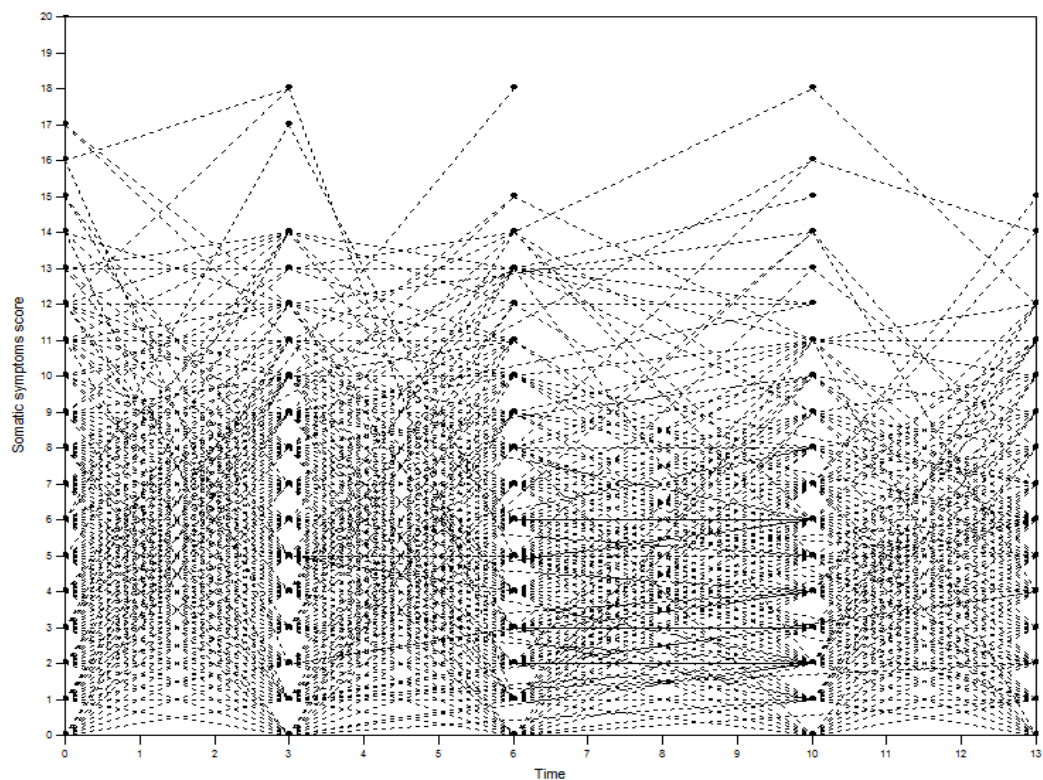
Supplementary Figure S5. Individual trajectories of depressed affect



Supplementary Figure S6. Individual trajectories of positive affect



Supplementary Figure S7. Individual trajectories of somatic symptoms



***CHAPTER 7: LONGITUDINAL ASSOCIATIONS BETWEEN LATE-LIFE
DEPRESSION SYMPTOMS AND COGNITIVE FUNCTIONING IN LATIN
AMERICAN COUNTRIES: A CROSS-LAGGED PATH ANALYSIS***

7.1 Introduction

Late-life depression symptoms co-occur with cognitive dysfunctions (Baudic, Tzortzis, Barba, & Traykov, 2004; Lockwood, Alexopoulos, & van Gorp, 2002; Sheline et al., 2006), but the direction of the effect remains unclear. Based on existing evidence it is not possible to conclude whether depression is a risk factor for cognitive decline, a psychological reaction to perceived cognitive deficits, or whether the co-occurrence of depression and cognitive dysfunctions in close temporal proximity reflects a common cause such as incipient dementia. Most of the previous studies investigated only unidirectional prospective effects - that is whether initial depression symptoms predict the course of cognitive functioning, or whether initial cognitive performance levels predict the course of depression. Even studies that tried to address problems of reverse causation by simultaneously examining both directions of the effect have yielded inconsistent findings. Some findings support one direction of the effect, whereby higher initial depression symptoms predicted accelerated cognitive decline, but initial cognitive performance did not predict changes in depression symptoms (Bunce, Batterham, Christensen, & Mackinnon, 2014; Gale, Allershand, Deary, & Team, 2012; Panza et al., 2009; Vinkers, Gussekloo, Stek, Westendorp, & van der Mast, 2004). Other findings support the opposite direction of the effect, whereby poorer initial cognitive performance predicted an increase in depression symptoms, but initial depression symptoms did not predict changes in cognitive performance (Jajodia & Borders, 2011; Perrino, Mason, Brown, Spokane, & Szapocznik, 2008). One study found bidirectional prospective associations between depression symptoms and cognitive functioning

(van den Kommer et al., 2013) (for a summary of these study findings please see Chapter 1, Table 4).

The direction of influence between depression symptoms and cognitive functioning may vary as a function of the follow-up duration. In the longitudinal LASA study described in Chapter 6, including a relatively long follow-up duration (13 years), I found a prospective effect of poor initial delayed recall performance on increasing depression symptoms, no prospective effect of initial depression symptoms on cognitive decline, and a synchronous association between increasing depression symptoms and declining processing speed (after accounting for relevant confounders) (Brailean et al., 2016). Examining the same research question in a study with a relatively short follow-up duration (as is the case with the 10/66 study) can help clarify the extent to which longitudinal associations between depression and cognitive functioning may vary as a function of the follow-up duration.

Emerging evidence suggests that associations between depression and cognitive functioning may vary as a function of the type of depression symptom experienced (the relevant literature on this topic was reviewed in Chapter 1). Cross-sectional studies of the Euro-D depression scale have distinguished between two depression symptom-dimensions: “motivation disturbance” and “affective suffering”, and they showed that symptoms of motivation disturbance are more strongly associated with verbal fluency impairment than affective suffering symptoms (Brailean, Guerra, Chua, Prince, & Prina, 2015; Castro-Costa et al., 2007; M. Prince et al., 1999). Other findings suggest that motivational symptoms of depression are dominant in the preclinical phase of Alzheimer Disease (Bartolini, Coccia, Luzzi,

Provinciali, & Ceravolo, 2005; Berger, Fratiglioni, Forsell, Winblad, & Backman, 1999), and in mild cognitive impairment (Kumar, Jorm, Parslow, & Sachdev, 2006), and that poor initial executive function and processing speed performance predict a stronger increase in motivational symptoms of depression than in mood symptoms (Kooistra et al., 2015). According to the depression-executive dysfunction hypothesis, the association between executive function/processing speed impairment and apathetic/motivational symptoms of depression may be due to ageing-related dysfunctions in fronto-striatal structures and cerebrovascular disease (Alexopoulos et al., 2005; Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002). The presence of motivational symptoms accompanied by executive function deficits may be associated with a more chronic course of cognitive dysfunctions and a higher risk of AD (Bartolini et al., 2005). There is currently insufficient evidence to conclude whether motivational symptoms of depression have stronger prospective associations with cognitive dysfunctions than other depression symptoms, and whether the effect is unidirectional or bidirectional.

In the current study I aimed to examine longitudinal bidirectional associations between depression symptoms and cognitive functioning (verbal fluency, immediate recall, and delayed recall). Depression symptoms were conceptualised both as a unitary concept (total Euro-D score) and as specific symptom-dimensions previously derived in factor analytic studies of Euro-D (motivation disturbance and affective suffering) (Brailean et al., 2015; M. Prince et al., 1999). The research questions are: (1) Is the prospective influence of depression symptoms on later cognitive function stronger than the prospective influence of cognitive function on later depression symptoms? (2) Does the magnitude and direction of the effect vary as a function of

the type of depression symptoms experienced and the cognitive abilities affected? Based on previous cross-sectional findings (Brailean et al., 2015; Castro-Costa et al., 2007), I expected that motivational symptoms of depression would show stronger longitudinal associations with cognitive dysfunctions (especially in the verbal fluency domain) than affective suffering symptoms.

7.2 Method

7.2.1 Participants

This study sample consisted of 11,461 respondents aged 65 and above from six low and middle income countries in Latin America (Peru, Venezuela, Mexico, Puerto Rico, Cuba, Dominican Republic) who were dementia free at the moment of the baseline assessments conducted by the 10/66 Dementia Research Group (M. Prince et al., 2007). In Peru and Mexico participants were recruited from both urban and rural catchment areas, whereas in all other countries only urban catchment areas were included. Response rates were high for baseline assessments, ranging between 80% in Venezuela and urban Puerto Rico to 90% in Dominican Republic. Follow-up data was collected 3 to 4 years later in all centres. Loss to follow-up rates were about 30% for the overall sample, ranging between 23% in rural Peru and urban Mexico and 39% in Dominican Republic. The main reason for attrition was mortality which accounted for 41% of dropout cases in the overall sample. Details on data collection, study design, and cohort characteristics are provided in Chapter 2.

7.2.2 Measures

Depression was assessed using the EURO–D, a depression scale developed based on the Geriatric Mental State (GMS; Copeland et al., 1976). Euro-D assesses 12 symptoms of depression (i.e., depressed mood, pessimism, suicidality, guilt, sleep, interest, irritability, appetite, fatigue, concentration, enjoyment and tearfulness) and the total score ranges from 0 to 12 (M. Prince et al., 1999). According to previous reports, Euro-D has good internal consistency and criterion validity (M. Prince, 1995). A score of 4 and above is considered to indicate depression symptoms of probable clinical significance (Castro-Costa et al., 2007; M. Prince et al., 1999). In the current study subscale scores for “motivation disturbance” (i.e., items: interest, enjoyment, concentration) and for “affective suffering” (i.e., all other items) were calculated based on the depression symptom dimensions previously established through factor analysis (Brailean et al., 2015).

Episodic memory was assessed by requiring participants to memorize and recall a list of 10 words. These words were presented verbally during 3 trials and participants were asked to repeat the words they remembered at the end of each trial. The total score on the three trials was used as a measure of immediate recall. After a delay during which participants completed a different task, they were asked to name again the words they remembered. The number of words recalled was used as a measure of delayed recall.

Verbal fluency was assessed using the animal naming task adapted from the Consortium to Establish a Registry for Alzheimer’s Disease (Vanderhill, Strauss, & Sherman, 2011). This task required participants to name as many animals as possible

over a period of one minute, and the total score was used as a measure of verbal fluency. Performance on the animal naming task is thought to rely upon multiple cognitive processes such as executive functioning, semantic memory, and language ability (Abwender, Swan, Bowerman, & Connolly, 2001; Henry & Phillips, 2006).

7.2.3 Statistical analyses

I used cross lagged path analysis (see Figure 1) to investigate bidirectional associations between overall depression symptoms and cognitive abilities (i.e., verbal fluency, immediate recall, delayed recall). A full cross-lagged model simultaneously estimates multiple effects:

a) Lagged effects (also known as stability or autoregressive effects) represent the regression of a variable on its own lagged score (i.e., cognitive performance at time 1 predicts cognitive performance at time 2; depression at time 1 predicts depression at time 2). Lagged effects refer to the stability of the rank ordering of individuals on a variable over time; coefficients closer to a value of 1 reflect greater stability (i.e., individuals who have higher depression scores at baseline tend to have higher depression scores at follow-up; individuals who have lower cognitive performance at baseline tend to have lower cognitive performance at follow-up). Lagged effects are based on the notion that previous traits or performance are the best predictor of current traits or performance.

b) Cross-lagged effects refer to the effect of a variable on an outcome at a later time point, controlling for the prior level of the outcome (i.e., depression at time 1 predicting cognitive performance at time 2, controlling for cognitive performance at time 1; or cognitive performance at time 1 predicting depression at time 2,

controlling for depression at time 1). The fact that cross-lagged effects are estimated simultaneously with lagged effects means that the variance in follow-up cognitive performance that can be predicted by baseline depression is the residual variance that remains after controlling for baseline levels of cognitive performance. Similarly, the variance in follow-up depression that can be predicted by baseline cognitive performance is residual variance that remains after controlling for previous levels of depression. If both cross-lagged regression coefficients are statistically significant this suggests reciprocal influences between depression symptoms and cognitive functioning, whereas if only one cross-lagged regression coefficient is statistically significant this suggests a unidirectional effect. By estimating both directions of the effect in the same model it is possible to determine the relative magnitude of the predictive associations between depression symptoms and cognitive functioning.

c) Occasion-specific correlations between depression and cognitive performance are estimated to control for the effect of unknown confounding variables. These are residual correlations because they capture the amount of shared variance in depression and cognition at the same measurement occasion, over and above the variance that is explained by autoregressive effects, cross-lagged effects, and model covariates (i.e., age, gender, education).

Because a model that estimates too many effects may result in capitalisation on chance (over-fitting) it is of interest to select the most parsimonious model, which is a model that estimates no more parameters than needed to achieve good model fit. The selection of the most parsimonious model is achieved by estimating competing models and comparing their fit by conducting chi-square difference testing. In the

context of cross-lagged models chi-square difference testing was performed to examine whether the model that examined bidirectional prospective associations between cognition and depression (Model 1) had better explanatory power (i.e., model fit) than models that examined unidirectional prospective effects (Model 2-3), or no prospective effects (Model 4). For each combination of cognitive ability (i.e., verbal fluency, immediate recall, delayed recall) and depression symptom-dimension (i.e., overall depression, affective suffering, and motivation symptoms) a set of four models were estimated.

Model 1 is a bidirectional model testing the hypothesis that baseline depression predicts follow-up cognition, and that baseline cognition also predicts follow-up depression. This model estimates: (a) two cross lagged effects (i.e., the effect of baseline cognition on follow-up depression and the effect of baseline depression on follow-up cognition), (b) two lagged effects (i.e., the effect of baseline cognition on follow-up cognition and the effect of baseline depression on follow-up depression), (c) occasion specific correlations between depression and cognition (within the baseline measurement and within the follow-up measurement), and (d) the effect of covariates (i.e., age, gender, education) on cognition and depression. Of note, because bidirectional cross-lagged models are saturated models (i.e., zero degrees of freedom) they would fit the data perfectly (i.e., chi square = 0).

Model 2 is a unidirectional model testing the hypothesis that baseline depression predicts follow-up cognition, but baseline cognition does not predict follow-up depression. This model estimates the cross-lagged effect of baseline depression on follow-up cognition, alongside with the lagged effects, the occasion specific correlations, and the effects of covariates.

Model 3 is a unidirectional model testing the hypothesis that baseline cognition predicts follow-up depression, but baseline depression does not predict follow-up cognition. This model estimates the cross-lagged effect of baseline cognition on follow-up depression, alongside with the lagged effects, the occasion specific correlations, and the effects of covariates.

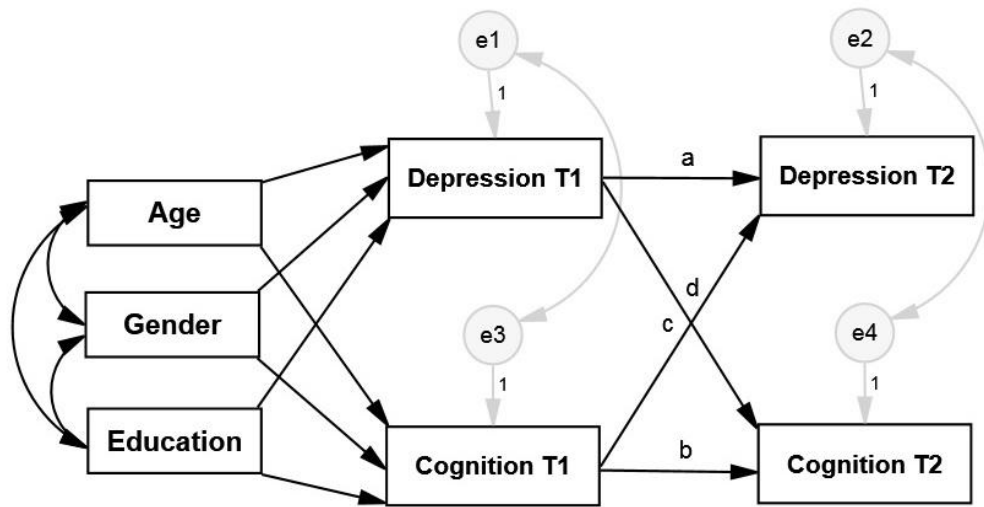
Model 4 is a model testing the hypothesis that there are no prospective associations between depression and cognition in either direction. This model includes only lagged effects, occasion specific correlations, and the effect of covariates.

Chi-square differences testing was calculated using the Satorra-Bentler Scaled Chi Square formula (Satorra, 2000) to compare the fit of Model 2-4 against the fit of Model 1. A chi square difference that attained $p < 0.05$ level was considered significant. Among models with similarly good model fit, the most parsimonious model (i.e., the model that estimates fewer effects) would be retained (Kline, 2005). If the unidirectional model fitted the data worse than the bidirectional model, then the bidirectional model would be retained. If the unidirectional model fitted the data similarly well as the bidirectional model, then the unidirectional model would be retained because it is considered more parsimonious.

The magnitude of cross-lagged effects (reflecting the association between a predictor and a later outcome adjusted for the lagged effects, the occasion-specific correlations and the influence of covariates) tends to be smaller than the bivariate correlation between a predictor and a later outcome (reflecting the association between two variables in the absence of adjustment for other variables). In the context of cross-lagged models the simultaneous estimation of multiple effects

reduces the proportion of variance in the outcome that is shared with the predictor leading to a reduced magnitude of the cross-lagged effects (e.g., a large proportion of variance in follow-up depression that is shared with baseline cognition is removed after controlling for previous levels of depression, for the concurrent associations between depression and cognition, and for the effects of age, gender and education on depression). Although no standard guidelines exist for interpreting the effect size of cross-lagged coefficients the difference between the magnitude of a bivariate correlation and the magnitude of a cross-lagged effect would be larger when the stability effect is larger (Adachi & Willoughby, 2015). For comparison purposes bivariate correlations between initial depression and later cognition and between initial cognition and later depression were also calculated.

Figure 1. Cross-lagged model illustrating bidirectional associations between depression symptoms and cognitive performance



Note: The model assumes that each variable predicts itself and the other variable over time. Models are adjusted for age, gender and education.

7.3 Results

Descriptive statistics for the overall study sample are presented in Table 1. Participants were aged 65 to 104 years at baseline, with a mean age of 74 years. Females represented 64% of the study sample. About 26% of participants had depression symptoms of probable clinical significance, as suggested by a Euro-D score of 4 or above (Castro-Costa et al., 2007; M. Prince et al., 1999). The dropout rate was 30% for the overall sample. Bivariate correlations between cognitive scores and depression scores are presented in Table 2. The Chi-square difference testing suggests that the bidirectional cross-lagged models generally fitted the data significantly better than the other models (with two exceptions which are discussed below). Results presented in Tables 3-5 are based on the bidirectional cross-lagged models (Model 1).

Table 3 presents findings from the cross-lagged models examining associations between *overall depression symptoms* (i.e., total Euro-D score) and each cognitive ability (verbal fluency, immediate recall and delayed recall), adjusting for age, gender and education. Stability paths for overall depression symptoms and cognitive abilities were statistically significant and indicated a moderate stability (ranging from $\beta = 0.39$ to $\beta = 0.42$) of the rank ordering of individuals on depression/cognition measures over time (i.e., individuals who score high at baseline tend to score high at follow up). Correlations between overall depression symptoms and each cognitive ability at baseline and at follow up were significant and of small magnitude (ranging from $\beta = -0.06$ to $\beta = -0.17$). Cross-lagged effects suggest statistically significant bidirectional associations of small magnitude between overall depression symptoms and each cognitive ability (ranging from $\beta = -0.02$ to $\beta = -$

0.06). Higher baseline depression levels predicted lower cognitive performance at follow up, and lower cognitive performance at baseline predicted higher depression scores at follow up.

Table 4 presents findings from the cross-lagged models examining the associations between *affective suffering symptoms* of depression and cognitive abilities (verbal fluency, immediate recall and delayed recall), adjusting for age, gender and education. Stability paths for affective suffering and cognitive abilities were statistically significant and of moderate magnitude (ranging from $\beta = 0.39$ to $\beta = 0.42$). Correlations between affective suffering and cognitive abilities at baseline and at follow up were statistically significant and of small magnitude (ranging from $\beta = -0.05$ to $\beta = -0.14$). With regard to cross-lagged paths, both directions of the effect were statistically significant and of small magnitude in the models that included verbal fluency and immediate recall (ranging from $\beta = -0.02$ to $\beta = -0.05$), indicating that higher baseline levels of affective suffering predicted poorer follow-up levels of verbal fluency/immediate recall, and poorer baseline levels of verbal fluency/immediate recall predicted higher follow-up levels of affective suffering. Only one direction of the effect was statistically significant in the model that included delayed recall, indicating that higher levels of affective suffering at baseline predicted lower levels of delayed recall at follow up ($\beta = -0.05$), whereas baseline levels of delayed recall did not predict follow-up levels of affective suffering. The bidirectional model for delayed recall and affective suffering did not fit the data better than the unidirectional model estimating the effect of initial affective suffering on later delayed recall. Therefore, the non-significant cross-lagged path (i.e., the effect of baseline delayed recall on follow-up affective suffering) was removed from

the model; this model modification did not alter the magnitude or significance of the other effects estimated.

Table 5 presents findings from the cross-lagged models that examined the association between *motivational symptoms* of depression and cognitive abilities (verbal fluency, immediate recall and delayed recall), adjusting for age, gender and education. Stability paths for motivational symptoms and cognitive abilities were statistically significant and of small ($\beta = 0.21$ for motivation symptoms) to moderate magnitude ($\beta = 0.39$ for verbal fluency). Correlations between motivational symptoms and cognitive abilities at baseline and at follow-up were statistically significant and of small magnitude ($\beta = -0.06$ to -0.17). With regard to cross-lagged paths, both directions of the effect were statistically significant and of small magnitude in models that included immediate and delayed recall ($\beta = -0.03$ to -0.05), indicating that higher baseline levels of motivational symptoms predicted poorer follow-up levels of immediate and delayed recall, and poorer baseline levels of immediate and delayed recall predicted higher follow-up levels of motivational symptoms. Only one direction of the effect was statistically significant in the model that included verbal fluency, indicating that lower levels of verbal fluency at baseline predicted higher motivational symptoms at follow-up ($\beta = -0.06$), whereas baseline levels of motivational symptoms did not predict follow-up levels of verbal fluency. The bidirectional model for verbal fluency and motivational symptoms did not fit the data significantly better than the unidirectional model estimating the effect of baseline verbal fluency on follow-up motivational symptoms. Therefore, the non-significant cross-lagged path (i.e., the effect of baseline motivational symptoms on

follow-up verbal fluency) was removed from the model; this model modification did not alter the magnitude or significance of the other effects estimated.

All the cross-lagged coefficients and the bivariate correlation coefficients between initial depression and later cognition and between initial cognition and later depression were of small magnitude. Due to the simultaneous estimation of stability effects and contemporaneous associations between depression and cognition, the magnitude of cross-lagged effects is smaller than the bivariate correlations between the earlier predictor and the later outcome.

Table 1. Descriptive statistics for the study sample

Baseline scores on covariates			Baseline scores on cognitive and depression measures			
	N	Mean		N	Mean	S.D.
Age	11454	74	Immediate recall	11461	14.5	4.2
			Delayed recall	11444	4.7	2.0
Gender	N	%	Verbal fluency	11461	15.8	5.6
			Depression (overall)	11438	2.3	2.3
Female	7334	64	Motivation symptoms	11370	0.3	0.7
Male	4129	36	Affective suffering	11294	2.0	1.9
			Follow-up scores on cognitive and depression measures			
Education	N	%		N	Mean	S.D.
None	1113	10	Immediate recall	7898	13.4	4.7
Some primary	3174	28	Delayed recall	7897	4.1	2.2
Complete primary	3427	30	Verbal fluency	7791	14.7	5.6
Completed secondary	2313	20	Depression (overall)	7372	2.1	2.2
College	1392	12	Motivation symptoms	7730	0.3	0.6
			Affective suffering	7895	1.8	1.9

Table 2. Bivariate correlations between cognitive scores and depression scores

	Dep T1	Dep T2	Mot T1	Mot T2	Aff T1	Aff T2	VF T1	VF T2	IR T1	IR T2	DR T1	DR T2
Dep T1	1.00											
Dep T2	0.43	1.00										
Mot T1	0.62	0.24	1.00									
Mot T2	0.25	0.64	0.22	1.00								
Aff T1	0.97	0.43	0.40	0.22	1.00							
Aff T2	0.43	0.97	0.21	0.41	0.43	1.00						
VF T1	-0.09	-0.13	-0.07	-0.11	-0.08	-0.11	1.00					
VF T2	-0.07	-0.19	-0.03	-0.17	-0.07	-0.16	0.46	1.00				
IR T1	-0.12	-0.10	-0.09	-0.10	-0.11	-0.08	0.40	0.30	1.00			
IR T2	-0.11	-0.21	-0.07	-0.20	-0.11	-0.18	0.33	0.49	0.51	1.00		
DR T1	-0.09	-0.09	-0.07	-0.10	-0.09	-0.07	0.37	0.29	0.71	0.45	1.00	
DR T2	-0.11	-0.18	-0.08	-0.20	-0.10	-0.15	0.31	0.48	0.45	0.77	0.48	1.00

Note: All correlations were statistically significant; Dep = Depression; Mot = Motivation disturbance; Aff = Affective suffering; VF = Verbal Fluency; IR = Immediate Recall; DR = Delayed Recall; T1 = baseline; T2 = follow-up

Table 3. Associations between overall depression symptoms and cognitive abilities

Model 1. Depression and verbal fluency		
<i>Stability paths</i>	β	S.E.
Verbal fluency T1 → Verbal fluency T2	0.39***	0.01
Depression T1 → Depression T2	0.42***	0.01
<i>Cross lagged paths</i>		
Depression T1 → Verbal fluency T2	-0.02*	0.01
Verbal fluency T1 → Depression T2	-0.06***	0.01
<i>Baseline correlations</i>		
Verbal fluency with depression	-0.06***	0.01
<i>Follow up correlations</i>		
Verbal fluency with depression	-0.14***	0.01
Model 2. Depression and immediate recall		
<i>Stability paths</i>	β	S.E.
Immediate recall T1 → Immediate recall T2	0.39***	0.01
Depression T1 → Depression T2	0.42***	0.01
<i>Cross lagged paths</i>		
Depression T1 → Immediate recall T2	-0.05***	0.01
Immediate recall T1 → Depression T2	-0.03*	0.01
<i>Baseline correlations</i>		
Immediate recall with Depression	-0.12***	0.01
<i>Follow up correlations</i>		
Immediate recall with Depression	-0.17***	0.01
Model 3. Depression and delayed recall		
<i>Stability paths</i>	β	S.E.
Delayed recall T1 → Delayed recall T2	0.39***	0.01
Depression T1 → Depression T2	0.42***	0.01
<i>Cross lagged paths</i>		
Depression T1 → Delayed recall T2	-0.06***	0.01
Delayed recall T1 → Depression T2	-0.02*	0.01
<i>Baseline correlations</i>		
Delayed recall with Depression	-0.09***	0.01
<i>Follow up correlations</i>		
Delayed recall with Depression	-0.13***	0.01

β = standardized coefficient; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$;

Table 4. Associations between affective suffering and cognitive abilities

Model 1. Affective suffering and verbal fluency		
<i>Stability paths</i>	β	S.E.
Verbal fluency T1 → Verbal fluency T2	0.39***	0.01
Affective suffering T1 → Affective suffering T2	0.42***	0.01
<i>Cross lagged paths</i>		
Affective suffering T1 → Verbal fluency T2	-0.02*	0.01
Verbal fluency T1 → Affective suffering T2	-0.06***	0.01
<i>Baseline correlations</i>		
Verbal fluency with Affective suffering	-0.05***	0.01
<i>Follow up correlations</i>		
Verbal fluency with Affective suffering	-0.13***	0.01
Model 2. Affective suffering and immediate recall		
<i>Stability paths</i>	β	S.E.
Immediate recall T1 → Immediate recall T2	0.39***	0.01
Affective suffering T1 → Affective suffering T2	0.42***	0.01
<i>Cross lagged paths</i>		
Affective suffering T1 → Immediate recall T2	-0.05***	0.01
Immediate recall T1 → Affective suffering T2	-0.02*	0.01
<i>Baseline correlations</i>		
Immediate recall with Affective suffering	-0.10***	0.01
<i>Follow up correlations</i>		
Immediate recall with Affective suffering	-0.14***	0.01
Model 3. Affective suffering and delayed recall		
<i>Stability paths</i>	β	S.E.
Delayed recall T1 → Delayed recall T2	0.39***	0.01
Affective suffering T1 → Affective suffering T2	0.42***	0.01
<i>Cross lagged paths</i>		
Affective suffering T1 → Delayed recall T2	-0.05***	0.01
Delayed recall T1 → Affective suffering T2	-0.02	0.01
<i>Baseline correlations</i>		
Delayed recall with Affective suffering	-0.08***	0.01
<i>Follow up correlations</i>		
Delayed recall with Affective suffering	-0.11***	0.01

β = standardized coefficient; * p < 0.05; ** p < 0.01; ***p < 0.001;

Table 5. Associations between motivation disturbance and cognitive abilities

Model 1. Motivation disturbance and verbal fluency		
<i>Stability paths</i>	β	S.E.
Verbal fluency T1 → Verbal fluency T2	0.39***	0.01
Motivation disturbance T1 → Motivation disturbance T2	0.21***	0.02
<i>Cross lagged paths</i>		
Motivation disturbance T1 → Verbal fluency T2	<-0.01	0.01
Verbal fluency T1 → Motivation disturbance T2	-0.06***	0.01
<i>Baseline correlations</i>		
Verbal fluency with Motivation disturbance	-0.06***	0.01
<i>Follow up correlations</i>		
Verbal fluency with Motivation disturbance	-0.13***	0.01
Model 2. Motivation disturbance and immediate recall		
<i>Stability paths</i>	β	S.E.
Immediate recall T1 → Immediate recall T2	0.39***	0.01
Motivation disturbance T1 → Motivation disturbance T2	0.22***	0.01
<i>Cross lagged paths</i>		
Motivation disturbance T1 → Immediate recall T2	-0.03**	0.01
Immediate recall T1 → Motivation disturbance T2	-0.04**	0.01
<i>Baseline correlations</i>		
Immediate recall with Motivation disturbance	-0.09***	0.01
<i>Follow up correlations</i>		
Immediate recall with Motivation disturbance	-0.17***	0.01
Model 3. Motivation disturbance and delayed recall		
<i>Stability paths</i>	β	S.E.
Delayed recall T1 → Delayed recall T2	0.39***	0.01
Motivation disturbance T1 → Motivation disturbance T2	0.22***	0.01
<i>Cross lagged paths</i>		
Motivation disturbance T1 → Delayed recall T2	-0.04***	0.01
Delayed recall T1 → Motivation disturbance T2	-0.05***	0.01
<i>Baseline correlations</i>		
Delayed recall with Motivation disturbance	-0.08***	0.01
<i>Follow up correlations</i>		
Delayed recall with Motivation disturbance	-0.15***	0.01

β = standardized coefficient; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$;

7.4 Conclusions

Using data from a large sample of older adults from Latin American countries and a multidimensional approach to late-life depression, this longitudinal study examined the direction of influence between an array of cognitive abilities (immediate recall, delayed recall and verbal fluency) and depression, conceptualised either as a unitary construct (total Euro-D score) or as specific symptom dimensions (motivation disturbance and affective suffering).

Overall depression symptoms showed significant bidirectional associations with all cognitive domains assessed, indicating that higher initial levels of depression predicted poorer subsequent cognition performance, and poorer initial cognitive performance predicted higher subsequent depression levels. Among previous studies that used similar follow-up durations (3 to 4 years) some found evidence supporting one direction of the effect, whereby higher initial depression levels predicted poorer subsequent levels of global cognitive function and delayed recall (Panza et al., 2009), processing speed and reaction time (Bunce et al., 2014). Other studies found evidence supporting the opposite direction of the effect, whereby poorer initial global cognitive function (Perrino, Mason, Brown, Spokane, & Szapocznik, 2008) and poor initial delayed recall performance (Jajodia & Borders, 2011) predicted higher subsequent levels of depression.

Affective suffering symptoms of depression showed significant bidirectional associations with verbal fluency and immediate recall performance. The association between affective suffering and delayed recall was unidirectional, indicating that higher levels of affective suffering at baseline predicted poorer delayed recall

performance at follow-up, whereas delayed recall performance at baseline did not predict affective suffering symptoms at follow-up. The current findings seem inconsistent with findings from the longitudinal LASA study which found that poorer initial delayed recall performance predicted a higher increase in depressed affect over time. Whereas LASA findings suggest that the increase in depressed affect may reflect a psychological reaction to perceived memory dysfunctions (Brailean et al., in press), findings from the current study suggest that affective suffering symptoms of depression may increase the risk of memory decline. The discrepancy between these findings may be due to differences between studies in the follow-up duration and in the specific depression symptoms assessed with the depressed affect subscale of CES-D (including only depressed affect symptoms) versus the affective suffering subscale of Euro-D (including a combination of depressed affect symptoms and somatic symptoms).

Motivational symptoms of depression showed significant bidirectional associations with immediate and delayed recall, but only unidirectional associations with verbal fluency performance. Poorer verbal fluency performance at baseline predicted higher levels of motivational symptoms at follow-up, whereas baseline levels of motivational symptoms did not predict follow-up levels of verbal fluency. In line with the depression executive-dysfunction hypothesis (Alexopoulos et al., 2005; Alexopoulos et al., 2002), and based on previous findings (Brailean et al., 2015; Castro-Costa et al., 2007; Kumar et al., 2006), I expected that motivational symptoms of depression would show stronger prospective associations with verbal fluency performance than affective suffering symptoms. However, the current findings did not provide support for this hypothesis. My findings add to the existing

literature by clarifying that verbal fluency dysfunctions drive changes in motivational symptoms of depression and not vice-versa. This direction of the effect is consistent with findings by Kooistra et al. (2015) indicating that older adults with poorer initial executive function and processing speed performance showed an increase in motivational symptoms of depression over seven years of follow-up. Although there is insufficient evidence to draw conclusions about the direction of influence between motivational symptoms of depression and cognitive dysfunctions, this association may vary as a function of the stage of cognitive impairment. Motivational symptoms of depression have been shown to predict a clinical diagnosis of AD better than other types of depression symptoms one year later (Bartolini et al., 2005) and three years later (Berger et al., 1999). Taken together these findings suggest that community dwelling older adults with subclinical cognitive deficits (affecting in particular the processing speed and executive function domains) are at greater risk of motivational symptoms of depression (based on findings from the current study and findings by Kooistra et al., 2015). Among persons who are in the preclinical stage of dementia the opposite direction of the effect may be more salient, whereby motivational symptoms precede a diagnosis of dementia in close temporal proximity (as suggested by the findings of Bartolini et al., 2005 and Berger et al., 1999). Motivational symptoms of depression may be part of a dementia prodrome.

Findings from the current study should be interpreted taking into account that all concurrent associations and prospective associations between depression symptoms/symptom dimensions and cognitive abilities were of small magnitude. The small magnitude of these associations may be due to the characteristics of the study sample including community dwelling older adults among whom only a small

percentage had potential cognitive impairment or clinically significant depression symptoms.

Strengths of this study include the large sample size, the use of a statistical analysis method that allows for a simultaneous examination of bidirectional associations between depression symptoms and cognitive functioning, and the fact that this examination was conducted in an under-researched population of older adults from low and middle income countries in Latin America. A limitation of this study is that findings are limited to community dwelling older adults and cannot be generalised to clinical populations. Moreover, the simultaneous estimation of bidirectional prospective associations between depression and cognition allows only to determine the relative size of predictive associations, and does not imply a causal effect. Finally, the symptom dimensions used in this study were conceptualised as “motivation disturbance” and “affective suffering” based on previous factor analytic findings which supported this factor structure of Euro-D (Brailean et al., 2015). Future studies aiming to clarify which symptoms of depression show stronger associations with cognitive dysfunctions could take a different approach by focusing either on individual symptoms (e.g., apathy) or on a different symptom clustering (e.g., mixed motivational and somatic symptoms may be more predictive of cognitive dysfunctions than pure mood-related symptoms).

To conclude, findings from this study support both directions of the effect between overall depression symptoms and various domains of cognitive functioning. The association between specific depression symptom dimensions and most cognitive domains was also bidirectional, with the only unidirectional effects

suggesting that higher initial affective suffering symptoms predicted a loss in delayed recall ability, whereas poorer initial verbal fluency predicted an increase in motivational symptoms of depression. Given the relatively short follow-up duration in this study, the manifestation of depression symptoms and cognitive dysfunctions in close temporal proximity may reflect the influence of shared aetiological mechanisms. More research is needed to clarify the changing profile of depression symptoms across the full spectrum of cognitive ageing, from mild cognitive dysfunctions to dementia.

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Chapter 8. RESEARCH CONCLUSIONS

8.1 Summary of the research investigations conducted

This thesis examined the role of cognitive reserve and depression symptoms in late-life cognitive inequalities. A key contribution of my research is in connecting disparate and seemingly paradoxical empirical findings from the cognitive reserve literature suggesting that higher educated individuals and later born cohorts exhibit higher initial cognitive performance, but similar or more rapid rates of cognitive decline in late life. In a further line of inquiry, my research investigated the complex interplay between late-life depression symptoms and various domains of cognitive functioning. Using a multidimensional approach to late-life depression, my thesis attempted to understand which symptoms of depression show stronger associations with cognitive dysfunctions, and what is the direction and timing of such influences. These inquiries were conducted in several stages.

The first line of investigation built on evidence suggesting that more recently born cohorts of older adults preserve better cognitive functioning in late life than earlier born cohorts of the same age, and that this may be due higher levels of education in the later born cohort. Cohort differences in initial levels and trajectories of cognitive performance and the role of education in accounting for these cohort effects were examined in a Dutch sample of older adults who participated in the LASA study.

The second line of investigation built on evidence suggesting that depression and cognitive dysfunctions co-occur in late life and that the nature and strength of this association may depend on the type of depression symptoms experienced. This research question was addressed in two psychometric studies, one conducted among

older adults in Latin American countries (10/66 study) and the other conducted among older adults in the Netherlands (LASA study). Specific depression symptom dimensions were established based on factor analytic studies of two depression scales (EURO-D and CES-D). Cross-sectional associations between latent depression dimensions and cognitive abilities were then examined in the context of adjustment for differential item functioning due to country of residence, age, gender, and cognitive function levels, to ensure that substantive conclusions are not affected by item response biases.

The third line of investigation informs on the longitudinal direction of influence and timing of the association between overall depression symptoms and several domains of cognitive functioning. Moreover, my research examined which specific symptom dimensions of depression co-occur, precede, follow, or accompany cognitive decline. These research questions were addressed in two longitudinal studies, one conducted among older adults in Latin American countries (10/66 study) and the other conducted among older adults in the Netherlands (LASA study).

My studies adopted a methodological approach aimed to reduce biases from three major challenges in observational studies: missing data (using ML estimation and pattern mixture modelling), measurement error (using latent variables modelling and adjustment for differential item functioning), and causal inference (by simultaneously examining bidirectional prospective associations between depression and cognition using cross-lagged path models and cross-domain latent growth curve models).

In this chapter I highlight the key findings and research conclusions, and I

discuss the strengths and limitations of the investigations conducted with a specific focus on the factors that limit the comparability of findings between the 10/66 study and the LASA study. I further discuss the implications of my findings for research, public health and clinical practice.

8.2 Conclusions about the influence of cognitive reserve on cohort differences in cognitive ageing

In Chapter 3, I examined the extent to which educational attainment (as a proxy for cognitive reserve) may explain cohort differences in initial levels of cognitive performance and in rates of cognitive change.

8.2.1 Key findings

Regardless of cohort, more highly educated persons performed better on all cognitive tasks. My findings suggest that the later born cohort showed better initial performance in some cognitive abilities (i.e., processing speed general cognitive performance and inductive reasoning), but not in other cognitive abilities (i.e., immediate recall and delayed recall). Educational attainment accounted for cohort differences in initial levels of general cognitive performance and inductive reasoning, but not processing speed. Depending on the cognitive domain assessed, later born cohorts showed either: (1) similar rates of cognitive decline (i.e., inductive reasoning and general cognitive performance), or (2) steeper rates of cognitive decline (i.e., processing speed), or (3) shallower rates of cognitive decline (i.e., immediate recall and delayed recall, but only between time 1 and time 3 when the same word list was administered). Educational attainment did not account for cohort differences in

cognitive decline in any ability, with the exception of immediate recall (from time 1 to time 3).

8.2.2 Strengths and limitations

A strength of this study is the examination of cohort differences in several domains of cognitive functioning in late life using a longitudinal design and a relatively large sample size. Another strength of this study relies in the analyses conducted (i.e., pattern mixture analysis, and a comparison of the missing data patterns, the reasons for dropout, and the predictors of dropout between cohorts), which helped to reduce concerns about the influence of attrition on conclusions about cohort differences in cognitive functioning. One of the limitations of this study is that educational attainment was the only proxy measure used for cognitive reserve. This research did not investigate whether other proxy measures for cognitive reserve, such as occupational attainment or involvement in cognitively stimulating activities, might also influence cohort differences in cognitive ageing. Moreover, this study is only informative about differences in cognitive functioning between cohorts born 10 years apart, aged 65 to 75 at baseline, with an average difference in educational attainment of 1 year of schooling, over a follow-up duration of 6 years. The influence of educational attainment on cohort differences in cognitive ageing was examined using a range of cognitive ability tests that are widely used in epidemiological studies of ageing. However, the methodological approach used in my study does not clarify whether education explains cohort differences in specific cognitive abilities “s”, or in the general cognitive factor “g”. Previous evidence suggests that longer schooling may help optimize specific cognitive abilities rather than the general cognitive ability

(Ritchie, Bates, & Deary, 2015). Future studies could investigate whether differences in cognitive performance between birth cohorts manifest at the general or at the domain-specific level of cognition. Finally, based on the current findings it is not possible to determine whether the rise in cognitive test scores across birth cohorts reflects genuine improvements in the cognitive abilities assessed by these tests, or whether this reflects merely an improvement in test-taking ability.

8.2.3 Implications for research

A crucial aspect of healthy ageing is cognitive health. Previous research suggests that cognitive test scores have increased across generations, and that cohort improvements in cognitive performance are maintained in late life, a finding known as *the Flynn effect* (Flynn, 1987). My findings add to the existing body of knowledge by providing information about the patterns and magnitude of cohort differences in cognitive ageing. These findings suggest that later born cohorts of older adults show better levels of cognitive performance, but not necessarily slower rates of cognitive decline, compared to earlier born cohorts.

There is a scarcity of research examining the various factors that contribute to cohort differences in cognitive ageing and the timing of their influence, but educational attainment may be one of the factors accounting for these cohort effects. Higher educational attainment helps build optimal levels of cognitive reserve and brain reserve which may extend the window of healthy cognitive ageing. The fact that more recently born cohorts of older adults had more years of schooling may explain their superior cognitive functioning in late life compared to earlier born cohorts of the same age. My study is one of the few that examined the extent to

which educational attainment can account for cohort differences in levels of cognitive performance and rates of cognitive decline in late life. My finding that higher educational attainment accounted for initial cohort differences in some domains of cognitive performance suggests that higher cognitive reserve (built through schooling) may give later born cohorts an initial edge in cognitive performance in late life. Due to better cognitive reserve, later born cohorts may be able to tolerate more ageing-related neuropathology before cognitive decline manifests. The finding that education did not account for cohort differences in rates of cognitive decline may suggest that, once a certain threshold on neuropathological burden is reached and brain reserve/cognitive reserve is exhausted, later born cohorts may experience similar or steeper cognitive decline compared to earlier born cohorts

There remains a need for studies adopting a life-course perspective to examine the timing of the influence of various factors on cohort differences in cognitive ageing. Factors such as educational attainment, occupational attainment, and participation in cognitively stimulating activities may contribute towards building cognitive reserve at different life stages. My findings suggest that cognitive reserve built earlier in life through education gives later born cohorts an initial edge in cognitive performance, but it does not help slow down their cognitive decline. Future studies could examine whether factors that contribute to cognitive reserve later in life (i.e., occupational attainment, cognitive stimulation) may slow down ageing-related decline in later born cohorts. Furthermore, the mechanisms through which higher cognitive reserve may help improve cognitive functioning in later born cohorts require further elucidation. For instance, higher cognitive reserve may either slow down neurodegenerative processes, or it may help later born cohorts tolerate

more ageing-related neuropathology before cognitive impairment/dementia manifest clinically (i.e., by increasing cognitive efficacy and brain plasticity). Evidence for the role of cognitive reserve in slowing down disease pathology is provided by studies showing that higher cognitive reserve is related to lower increases in cerebrospinal fluid biomarkers of AD with older age (Almeida et al., 2015), as well as lower β -amyloid accumulation in the brain among ApoE4 carriers (Wirth, Villeneuve, La Joie, Marks, & Jagust, 2014). Evidence for the role of cognitive reserve in compensating for neurodegenerative burden and delaying the clinical manifestation of cognitive deficits comes from studies showing that, for a given level of cognitive performance, persons with higher cognitive reserve show greater white matter hyperintensities volume (i.e., higher neuropathological burden) than persons with lower cognitive reserve (Brickman et al., 2011). Understanding the mechanisms through which lifetime cognitive reserve influences cognitive functioning in old age holds implications for extending the window of healthy cognitive ageing.

8.2.4 Implications for public health and clinical services

If the demographic shift towards older populations is accompanied by a replacement of less educated earlier born cohorts with more educated later born cohorts, this could mean that the average level of cognitive performance at the population level remains stable or improves across generations, despite population ageing. Therefore, later born cohorts may not spend more years of life in poor cognitive health despite having higher life expectancy than earlier born cohorts. Previous projections suggest that a continuation of cohort improvements in cognitive performance that is at least a third of that observed in the past (2002-2008) could

offset the negative effects of population ageing until 2042 (Skirbekk, Stonawski, Bonsang, & Staudinger, 2013). This effect was found both in a rapid-ageing scenario and in a slow-ageing scenario (although the effect was stronger in the slow-ageing scenario) (Skirbekk et al., 2013).

Promoting a cognitively active lifestyle could help extend the window of healthy ageing and reduce the costs involved in the health and social care of persons with cognitive impairment and dementia. Understanding the role of cognitive reserve in cohort differences in cognitive ageing has potential implications for cognitive optimisation interventions. These interventions may be effective in reversing or slowing down cognitive decline (Ball et al., 2002; Kramer, Bherer, Colcombe, Dong, & Greenough, 2004; Li et al., 2016; Schaie, Willis, & Caskie, 2004), as well as improving functional outcomes (Willis, Tennstedt, Marsiske, & et al., 2006), and quality of life in older adults (Wolinsky et al., 2006).

8.3 Conclusions about the cross-sectional associations between latent depression dimensions and cognitive abilities

Chapter 4 and Chapter 5 examined cross-sectional associations between specific latent depression dimensions (i.e., derived through factor analysis) and specific cognitive abilities, while tackling concomitant psychometric issues such as the validity of the latent depression constructs across countries, and the presence of differential item functioning due to age, gender and cognitive function levels. These aims were achieved in two separate studies, one using the LASA dataset and the other using the 10/66 dataset.

8.3.1 Key findings

LASA study

The study conducted using the LASA dataset (Chapter 4) found that depression, as measured by CES-D in a sample of Dutch older adults, can be interpreted in terms of four domains: depressed affect, positive affect, somatic symptoms and interpersonal difficulties. This factor structure is consistent with previous reports (Beekman, van Limbeek, Deeg, Wouters, & van Tilburg, 1994; Radloff, 1977; Shafer, 2006). Higher levels of somatic symptoms of depression were associated with lower levels of inductive reasoning and processing speed. Higher levels of depressed affect were associated with lower levels of inductive reasoning. Positive affect and interpersonal difficulties were not associated with any of the cognitive abilities assessed. Differential item functioning effects due to age and gender were of small magnitude. Women were more likely to report crying spells, sleep disturbance, and feeling as good as others. Older persons reported more loneliness and less hope about the future. There was no differential item functioning due to cognitive function levels, which suggests that CES-D items measure the same depression constructs in persons with different levels of cognitive functioning. Adjusting for DIF effects due to age and gender did not alter substantive conclusions about the association between depression symptom dimensions and cognitive abilities.

10/66 study

Consistent with previous reports, the study conducted using the 10/66 dataset (Chapter 5) found that depression, as measured by EURO-D in a sample of older adults from six Latin American countries consists of two dimensions: motivation disturbance and affective suffering (Castro-Costa et al., 2007, 2008; Prince, Beekman, et al., 1999; Prince, Reischies, et al., 1999). The factor structure fitted the data well in each Latin American country and in the overall sample. Delayed recall performance was similarly associated with affective suffering and motivation disturbance, whereas verbal fluency performance was more strongly associated with motivation disturbance. Females had significantly higher levels of affective suffering and motivation disturbance symptoms than males. Age did not influence the level of affective suffering and motivational symptoms. Differential item functioning effects suggest that males were more likely to report irritability than females. No other DIF effects were found due to age, gender or cognitive function levels. Although complete measurement invariance could not be assumed across countries, DIF effects were small and adjusting for them did not affect substantive conclusions regarding the association between cognitive abilities and depression dimensions. These findings suggest that EURO-D has good construct validity and that it can be appropriately used for cross-cultural comparisons, as well as across age, gender and cognitive function levels.

8.3.2 Strengths and limitations

Notable strengths of the studies presented in Chapter 4 and Chapter 5 are the large sample sizes and the use of an analytic strategy involving latent variable modelling which can account for measurement error and estimate differential item functioning effects (i.e., due to age, gender, cognitive function levels, and country of residence), while simultaneously investigating associations between cognitive abilities and latent depression dimensions.

My studies employed a range of cognitive ability tests which are widely used in epidemiological studies of ageing and which are designed to measure specific domains of cognition. Although tests of specific cognitive abilities do measure those abilities, they also reflect an underlying general intelligence factor “g”, which was not captured with the methodological approaches employed in this thesis. Future studies using a bi-factor model could help clarify the relation between specific cognitive domains and depression symptoms over and above the general factor “g”. Producing satisfactory bi-factor models would require a larger and more diverse set of cognitive tests than the ones used in my studies, ideally assessing both fluid and crystallised abilities and including multiple tests for each cognitive domain. If the cognitive domains of interest are not comprehensively assessed by the available set of cognitive tests the content validity of the general cognitive factor may be questionable, and the interpretation of specific factors may be challenging (i.e., specific factors may emerge as method effects reflecting spurious correlations between items rather than theoretically meaningful domains of cognition).

The limitations of the LASA study and the 10/66 study were discussed in the respective chapters. This section will focus on discussing differences between the LASA study and the 10/66 study in the depression symptom dimensions and cognitive abilities assessed. While these differences between studies provided the opportunity for a richer investigation of the patterns of association between specific depression symptom clusters and various domains of cognitive functioning, they limit the comparability of the study findings. Both the CES-D and the EURO-D are comprehensive in assessing the symptoms of depression used by DSM-V to ascertain whether a person meets the criteria for a diagnosis of MDD (except for “thoughts of death” which are not assessed by CES-D). However, the CES-D and the Euro-D differ in the number of items and their content, perhaps accounting for the different depression symptom dimensions previously established in factor analytic studies. The LASA study uses the CES-D depression scale consisting of 20 items, whereas the 10/66 study uses the EURO-D depression scale consisting of 12 items. In the LASA study depression symptom dimensions were based on the original factor structure of CES-D which teases out clusters of somatic symptoms, depressed affect, positive affect and interpersonal difficulties (Radloff, 1977). In the 10/66 study depression symptom dimensions were based on the original factor structure of EURO-D which teases out a cluster of motivation disturbance symptoms and a cluster of affective suffering symptoms (Castro-Costa et al., 2007, 2008; Prince, Beekman, et al., 1999; Prince, Reischies, et al., 1999). The somatic subscale of CES-D consists of a mix of somatic symptoms (e.g., My appetite was poor; My sleep was restless) and motivational symptoms (e.g., I could not get "going"; I had trouble keeping my mind on what I was doing; I felt that everything I did was an effort),

whereas the affective suffering dimension of the EURO-D consists of a mix of depressed mood (e.g., depression, pessimism, tearfulness, guilt) and somatic symptoms of depression (e.g., appetite, sleep disturbance). Moreover, the EURO-D and the CES-D scales differ in the way somatic symptoms were rated. Interviewers who administered the Geriatric Mental State package (from which the EURO-D depression scale was derived) were instructed to only rate somatic symptoms of depression that were due to psychological factors and not those that were due to physical problems, on the basis of supplementary clarifying questions (e.g., sleeping problems were rated if they were due to altered mood and thoughts and not if they were due to physical conditions or noise). The CES-D questionnaire does not distinguish between the physical or psychological causes of somatic symptoms. Moreover, the research conclusions obtained may be affected by differences between the CES-D and the EURO-D depression scales in their ability to capture depression cases and in their association with common risk factors for depression (Courtin, Knapp, Grundy, & Avendano-Pabon, 2015). The use of different cognitive measures in the LASA study and the 10/66 study may also limit the comparability of findings between studies. Finally, the comparability of findings between the LASA study and the 10/66 study may be limited by the different cultural settings.

Although the above mentioned differences limit the direct comparability of study findings, they allow for a richer examination of the differential association between cognitive functioning and specific depression symptom clusters. Building on previous research, I was able to examine hypotheses that motivational symptoms of depression (i.e., EURO-D) or mixed somatic and motivational symptoms (i.e.,

CES-D) may show stronger associations with cognitive dysfunctions than other symptoms of depression.

8.3.3 Implications for research

Findings from the two studies presented in Chapter 4 and Chapter 5 support a differential association between cognitive abilities and latent depression dimensions in late life. Motivational symptoms of depression were more strongly associated with verbal fluency dysfunction than affective suffering symptoms in the cross-sectional 10/66 study. The somatic dimension of CES-D (consisting of a combination of somatic and motivational symptoms) was the only symptom dimension that showed associations with processing speed dysfunction in the cross-sectional LASA study. Taken together, these findings provide indirect support for the “depression-executive dysfunction hypothesis” which posits that late-life depression can present as motivation-related symptoms (i.e., psychomotor retardation, reduced interest in activities, apathy, mild vegetative symptoms) driven by ageing-related decline in executive functions (Alexopoulos, 2005). Symptoms of depressed affect (LASA study) and affective suffering (10/66 study) were also negatively associated with cognitive performance. These findings may suggest a psychological reaction to perceived cognitive dysfunctions, but this interpretation remains speculative given the cross-sectional nature of the studies. My findings also suggest that symptoms of positive affect and interpersonal difficulties were not related to cognitive dysfunctions in old age (LASA study). More research is needed to inform on potential aetiological mechanisms underlying the co-occurrence of cognitive dysfunctions with specific depression symptom profiles in late life.

Conclusions regarding the differential association between cognitive functioning and specific depression symptom dimension are limited by the scarcity of studies adopting a dimensional approach to depression, as well as by methodological differences between these studies in terms of the latent depression dimensions derived from factor analytic studies of different depression scales. Future research could aim to harmonise measures of depression in order to derive similar depression symptom dimensions and to examine their differential associations with various cognitive abilities. Rational harmonisation could be achieved by extracting semantically matched items from various depression scales (e.g., CES-D: “I had trouble keeping my mind on what I was doing”; EURO-D: “I had concentration difficulties”), standardising the item scores, and constructing short scale or subscale scores based on semantically comparable items (Gatz et al., 2015). Configural harmonisation could be achieved by deriving conceptually similar factor scores from different depression measures and standardising the factor scores. A high correlation between the standardised factor scores of different depression measures would indicate that the symptom dimensions assessed are similar across depression measures (Gatz et al., 2015). Empirical harmonisation could be achieved using IRT approaches to match the raw scores of different depression measures with the same latent trait score value (Gatz et al., 2015).

8.3.4 Implications for public health and clinical services

Depression screening should take into account the heterogeneous presentation of depression in older adults, with a special focus on the presence of somatic and motivational symptoms of depression which may be more strongly associated with cognitive dysfunctions than other types of depression symptoms. Depression items

assessing symptoms such as loss of interest, concentration difficulties, lack of enjoyment, psychomotor retardation, or sleep problems may capture common variance that is due to cognitive impairment in aspects such as executive function and processing speed. Older adults with executive dysfunction may be less responsive to antidepressant treatments (Alexopoulos et al., 2005; Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002; Alexopoulos et al., 2000a; Kalayam & Alexopoulos, 1999; Potter, Kittinger, Wagner, Steffens, & Krishnan, 2004), and they may show higher rates of depression relapse and recurrence (Alexopoulos et al., 2000b). The pathways linking depression to persistent cognitive dysfunctions may depend on depression symptom profiles, aetiology, and comorbidities (Butters et al., 2008). Findings from this thesis suggest that a multidimensional approach to late-life depression could be useful in informing on cognitive functioning among older adults with specific depression symptom profile, and this in turn could form a basis for developing novel diagnostic and treatment approaches for late-life depression.

8.4 Conclusions about the longitudinal associations between overall depression symptoms/specific depression dimensions and cognitive abilities

Chapter 6 and Chapter 7 examined the direction of influence between various domains of cognitive functioning and depression symptoms/symptom dimensions in two separate studies, one using the LASA dataset and the other one using the 10/66 dataset.

8.4.1 Key findings

LASA study

The study based on the LASA dataset used cross-domain latent growth curve modelling to simultaneously examine the effect of initial depression symptoms on cognitive trajectories, the effect of initial cognitive performance on depression trajectories, as well as correlations between depression trajectories and cognitive trajectories. Longitudinal associations with cognitive functioning were examined using depression conceptualised as a unitary construct (i.e., overall CES-D score), as well as specific depression symptom clusters previously established through factor analysis (i.e., depressed affect, positive affect and somatic symptoms).

- Depression as a risk factor for cognitive decline

Baseline levels of depressed affect, positive affect, somatic symptoms or overall depression symptoms (total CES-D score) did not influence the rate of cognitive decline. These findings do not support the hypothesis that depression symptoms may be a risk factor for cognitive decline.

- Depression as a psychological reaction to cognitive dysfunctions

Poor delayed recall performance at baseline predicted an increase in overall depression symptoms as well as a specific increase in depressed affect, but it was not associated with changes in somatic symptoms or positive affect. These findings suggest that depression symptoms may increase in reaction to perceived memory dysfunctions.

- Associations between changes in cognitive performance and changes in depression symptoms

A higher increase in depression symptoms over time was associated with steeper decline in processing speed, inductive reasoning and immediate recall, but only the association with processing speed remained statistically significant after controlling for relevant confounders. A higher increase in somatic symptoms of depression was associated with steeper decline in processing speed over time. These findings support a dynamic longitudinal association between declining cognitive performance and increasing depression symptoms.

10/66 study

The 10/66 study used cross-lagged path analysis to simultaneously examine the effect of baseline depression levels on follow-up cognitive performance levels, and the effect of baseline cognitive performance levels on follow-up depression levels. Cross-lagged associations with cognitive functioning were examined using depression conceptualised as a unitary construct (i.e., total EURO-D score), as well as specific depression symptom dimensions previously established through factor analysis (i.e., motivation disturbance, affective suffering).

- Depression as a risk factor for cognitive decline

Higher baseline levels of overall depression symptoms and affective suffering symptoms were associated with poorer immediate recall, delayed recall, and verbal fluency performance at follow-up. Higher baseline levels of motivational symptoms were associated with poorer follow-up levels of immediate and delayed

recall, but not verbal fluency. These findings support the hypothesis that higher initial depression symptoms may increase the rate of cognitive decline.

- Depression as a psychological reaction to cognitive dysfunctions

Poorer initial levels of immediate recall, delayed recall and verbal fluency were related to higher follow-up levels of motivational symptoms and overall depression symptoms. Poorer initial levels of immediate recall and verbal fluency, but not delayed recall, were related to higher follow-up levels of affective suffering symptoms. These findings support the hypothesis that poorer initial cognitive performance may increase the level of depression symptoms, perhaps as a psychological reaction to perceived cognitive dysfunctions.

8.4.2 Strengths and limitations

Strengths of these studies include the relatively large sample size and the use of statistical methods that allow to examine bidirectional prospective associations as well as synchronous longitudinal associations between specific dimensions of late-life depression and specific cognitive abilities. Moreover, the different follow-up duration between the 10/66 study (3 years) and the LASA study (13 years) provided a better understanding of the possible impact of timing of assessments on the longitudinal associations between depression symptoms and cognitive functioning.

My studies examined longitudinal associations between levels of cognitive performance and levels of depression symptoms among community dwelling older adults. In both the 10/66 study and the LASA study depression symptoms were assessed on a continuum of severity, and only a small percentage of participants met

criteria for probable clinical depression. In the 10/66 study 25% of the sample have probable clinical depression based on a cut-off score of 4 and above on the Euro-D, whereas in the LASA study, 16% of the sample had probable clinical depression based on a cut-off score of 16 and above. Cognitive functioning was also assessed on a continuum, with only 11% of participants meeting criteria for potential cognitive impairment based on a cut-off score of 23 and below on the MMSE. Given my samples composition, it should be acknowledged that study conclusions are rather applicable to the non-pathological range of the cognitive ageing spectrum. Another limitation of these studies is that the methods used can only inform on the relative magnitude of the prospective associations between depression and cognition, without implying a true causal effect. Moreover, given that the 10/66 study used a short follow-up duration whereas the LASA study used a long follow-up duration, findings from the two studies can not be directly compared in terms of the timing of the association between depression symptoms and cognitive abilities.

Other study limitations of these studies were addressed in more details in the respective chapters. This section will further focus on discussing a number of factors that may limit the comparability of findings between the LASA study and the 10/66 study. Besides differences between studies in the assessment of depression symptom dimensions and cognitive abilities (see section 8.2.2), the two studies differed in the follow-up duration and the number of repeated measurements, leading to the choice of different longitudinal analysis methods. This may have impacted on conclusions regarding the longitudinal associations between depression symptoms and cognitive functioning across the two studies. The LASA study included five repeated measurements of depression and cognition (over 13 years of follow-up).

This made possible the use of cross-domain latent growth curve models to investigate associations between initial levels of depression symptoms/symptom dimensions and changes in cognition, associations between initial levels of cognition and changes in depression symptoms/symptom dimensions, and associations between changes in cognition and changes in depression symptoms/symptom dimensions. The 10/66 study included two measurements of depression and cognition (over 3 years of follow-up). Latent growth curve models could not be used in the 10/66 study because they require a minimum of three repeated measurements to estimate linear trajectories. Instead, bidirectional prospective associations between depression symptoms/symptom dimensions and cognitive abilities were examined using cross-lagged path analysis. In autoregressive models change over time is considered in terms of the current value of each variable depending on its prior value; lagged and cross-lagged effects are calculated for the overall sample and not for each person in the sample. In latent growth curve models the current value of each variable does not depend on its prior value, and instead repeated measures of a variable are used to calculate the intercept and slope for each individual in the sample (Bollen & Curran, 2004). Therefore, the above-mentioned differences between methods should be taken into consideration when comparing findings from the LASA study with findings from the 10/66 study regarding the longitudinal associations between depression and cognition.

8.4.3 Implications for research

There is a wealth of research indicating that depression co-occurs with cognitive dysfunctions in late life, but the nature, direction and timing of the effect

remains unclear. The longitudinal studies presented in this thesis add to the literature by examining bidirectional associations between overall depression symptoms and cognitive functioning. My research advances current knowledge of the relation between depression and cognition by examining which symptom-dimensions of depression may be more strongly associated with poor cognitive functioning, what is the direction of the effect, and how this effect may vary as a function of when assessments of depression and cognition are made.

Effect of depression on cognition

With respect to the prospective effect of depression on cognition, my findings suggest that initial depression symptoms may be a risk factor for cognitive decline over a relatively short follow-up duration (i.e., 10/66 study), but not over a relatively long follow-up duration (LASA study). In the 10/66 study (3 years of follow-up) higher overall depression symptoms (total EURO-D score) and symptom dimensions (i.e., affective suffering, motivation disturbance) at baseline predicted faster cognitive decline in most cognitive abilities. The only exception was the lack of an association between baseline motivation disturbance and follow-up verbal fluency performance. On the contrary, in the LASA study (13 years of follow-up) higher overall depression symptoms (total CES-D score) and symptom dimensions (i.e., depressed affect, somatic symptoms, positive affect) at baseline did not predict an accelerated rate of cognitive decline. The findings that depression symptoms precede cognitive decline over a short follow-up duration (10/66) but not over a long follow-up duration (LASA study) may suggest either that depression is a proximal risk factor for cognitive decline, or that the same neurodegenerative mechanisms underlie the occurrence of both depression symptoms and cognitive decline.

Effect of cognition on depression

With respect to the prospective effect of cognition on depression, my findings suggest that poor initial cognitive performance predicted an increase in overall depression symptoms as well as an increase in specific symptoms of depression over a relatively short follow-up duration (10/66 study). The only exception was the lack of an association between baseline delayed recall performance and follow-up levels of affective suffering.

Over a relatively long follow-up duration (LASA study) poor baseline delayed recall performance (but not other cognitive abilities) predicted an increase in overall depression symptoms as well as an increase in depressed affect over time, suggesting a potential psychological reaction to perceived memory dysfunctions. Older adults may notice their memory failure more easily than other cognitive dysfunctions; memory failures may cause difficulties in daily living and related distress, leading to an increase in depressed affect.

The role of subjective memory complaints in the relation between objective memory dysfunctions and depression symptoms was not addressed in my thesis, and it remains an important topic for future research. Memory complaints are reported by 20% to 50% of persons aged 65 and above (Jonker, Geerlings, & Schmand, 2000). Whereas older people without cognitive impairment are quite accurate in estimating their memory functioning, awareness of memory dysfunctions may be impaired among persons with MCI and AD (Vogel et al., 2004). Moreover, there is evidence that subjective memory complaints correlate more strongly with depression symptoms than with objective cognitive performance (Minett, Da Silva, Ortiz, & Bertolucci, 2008). Future studies could compare subjective memory complaints with

objective testing of memory difficulties or informant ratings of memory problems to determine the extent to which older adults make accurate appraisals of their memory difficulties at different stages of cognitive impairment. More research is needed to clarify whether subjective memory complaints reflect a specific assessment of memory difficulties (Podewils, McLay, Rebok, & Lyketsos, 2003), or rather an evaluation of general cognitive ability (Clement, Belleville, & Gauthier, 2008). Finally, the extent to which the awareness of memory difficulties is influenced by depression symptoms needs further elucidation.

Associations between changes in depression and changes in cognition

The synchronous association between changes in cognition and changes in depression could only be examined in the LASA study (due to the number of repeated assessments available). These findings suggest that increasing depression symptoms (total CES-D score) were associated with declining performance in immediate recall, processing speed and inductive reasoning, but only the association with processing speed remained statistically significant after adjusting for relevant confounders. Declining processing speed was also associated with a specific increase in somatic symptoms of depression. The finding that persistent somatic symptoms of depression, but not initial symptoms, were related to cognitive decline may suggest that a chronic mechanism underlies this association (e.g., neurodegenerative processes characteristic of prodromal dementia).

Other considerations

Although my findings suggest a differential longitudinal association between depression symptom dimensions and cognitive abilities, this research does not clarify whether different groups within a larger population may have different trajectory classes of cognitive functioning and depression functioning. Emerging evidence suggests an increased risk of dementia in persons who experience chronic depression (i.e., increasing trajectory) but not in those who experience transient depression (i.e., remitting or relapsing trajectory) (Kaup et al., 2016; Mirza et al., 2016). Future studies could use latent class growth curve modelling to examine whether older adults with different trajectory classes (e.g., chronic, remitting, relapsing depression) of specific depression symptom-dimensions (e.g., depressed affect, positive affect, somatic symptoms) present an accelerated rate of cognitive decline and an increased risk of cognitive impairment and dementia.

My findings on the association between depression and cognitive functioning should be interpreted in the context of adjustment for educational attainment. My research does not clarify whether the longitudinal association between depression symptoms and cognitive functioning may vary as a function of educational attainment. The synergistic effects of depression and educational attainment on cognitive ageing deserve further exploration.

8.4.4 Implications for public health and clinical services

The combination of depression symptoms and cognitive dysfunctions is frequent in older adults, and is present in about 25% of community dwelling older adults aged 85 and above (Arve, Tilvis, Lehtonen, Valvanne, & Sairanen, 1999).

Some depression symptoms-clusters may share a common aetiology with cognitive impairment (e.g., vascular dementia, inflammatory processes), whereas others may have an independent aetiology but may influence the threshold of manifestation of cognitive dysfunctions. Understanding the web of causation between depression symptoms and cognitive dysfunctions could help clarify the aetiological mechanisms underlying these associations, and it could guide treatment approaches and help predict cognitive outcomes among depressed older adults.

If certain cognitive dysfunctions influence the course of depression, then interventions aimed at remedying cognitive dysfunctions, or mitigating their impact, could ameliorate depression symptoms. For instance, findings from the LASA study indicate an increase in depressed affect and overall depression symptoms among persons with poor initial delayed recall performance. Memory dysfunctions may cause difficulties in daily living and related distress, leading to an increase in depressed affect as a psychological reaction to perceived memory failure. There may be potential for memory training interventions to remedy cognitive dysfunctions and ameliorate depression symptoms. A meta-analysis of nearly 50 years of memory training studies concluded that memory can be improved among community-dwelling older adults (Gross et al., 2012), though this advantage may not generalize to untrained cognitive abilities such as reasoning or arithmetic (Melby-Lervag & Hulme, 2013). Among older adults with mild to moderate AD or vascular disease cognitive training may be ineffective in improving cognitive performance (for a systematic literature review see Bahar-Fuchs, Clare, & Woods, 2013), but cognitive rehabilitation may lead to more positive ratings of memory performance (Clare et al., 2010).

There is a scarcity of studies that examined the effect of memory training on depression symptoms among older adults. A multi-facet intervention consisting of memory training, information about memory functioning and strategies, and social interaction helped improve objective and subjective memory ability, and reduce depression symptoms among older adults (Winningham et al., 2003). Multidisciplinary rehabilitation programs consisting of memory training alongside with other intervention components (i.e., computer-assisted cognitive stimulation, expressive activities, physiotherapy, physical training) may be effective in maintaining cognitive function and reducing depression symptoms among persons with mild AD and cognitive impairment no dementia (CIND) (Santos et al., 2015; Viola et al., 2011). Given the multi-facet nature of these interventions, it is not possible to determine which component of the intervention may have played an active role in reducing depression symptoms. The mechanisms through which memory training may help improve depression symptoms remain to be investigated, but one potential mechanism may be an improvement in perceived cognitive efficacy.

Findings from the LASA study indicate that increasing somatic and motivational symptoms of depression were associated with accelerated processing speed decline. Further research is needed to establish whether older adults showing persistent somatic and motivational symptoms of depression may be at increased risk of accelerated cognitive decline and dementia. Referring persons with such a symptom profile for a comprehensive evaluation of neuropsychological function may help improve the early diagnosis of dementia. This could allow patients to better

benefit from treatment and support, to plan for the future, and preserve better quality of life.

Taken together, my findings suggest that depression symptoms and cognitive dysfunctions manifest in close temporal proximity. This is evidenced by synchronous longitudinal associations between depression symptoms and processing speed over a long follow-up duration, and by bidirectional prospective associations between depression symptoms and cognitive abilities over a short follow-up duration. These findings may encourage the development of treatment approaches that could simultaneously improve both conditions. For instance, behavioural interventions (e.g., structuring activities and using probes to initiate behaviour) and pharmacological interventions (e.g., agents acting on frontostriatal neurotransmitter systems) could remedy executive dysfunction and processing speed deficits, as well as ameliorate symptoms of depression (Alexopoulos, Buckwalter, et al., 2002).

8.5 Closing remarks

My thesis examined the role of cognitive reserve in accounting for cohort differences in cognitive ageing, and the interplay between cognitive functioning and depression in late life.

First, my findings suggest that cognitive reserve built through schooling may offer later born cohorts an initial edge in certain domains of cognitive performance in late life (i.e., processing speed, inductive reasoning, general cognitive ability). This initial edge in cognitive performance is maintained during the ageing process for cognitive abilities such as general cognitive performance and inductive reasoning, as evidenced by similar rates of decline between cohorts. The initial edge in cognitive

performance is lost for abilities such as processing speed, as evidenced by faster rates of cognitive decline in the later born cohort. My findings suggest that educational attainment does not have a clear role in accounting for cohort differences in cognitive ageing.

Second, my research strengthens the foundation for a multidimensional approach to late-life depression. The heterogeneity of late-life depression in terms of symptom presentations, aetiologies, and co-morbidities may mask important associations with cognitive dysfunctions that are due to specific symptom clusters of depression rather than overall depression symptoms. My findings suggest that cognitive performance on tests of executive function and processing speed may be more strongly related to motivational and somatic symptoms than to other symptoms of depression. Motivational and somatic symptoms of depression may capture common variance that is due to cognitive impairment in areas such as executive function and processing speed.

Third, my research contributes to the field by clarifying the direction and timing of the longitudinal association between depression symptoms and cognitive functioning. When conceptualizing depression as a unitary construct, my findings suggest that depression symptoms do not precede, but rather accompany, the occurrence of cognitive decline in older adults. This is suggested by the synchronous longitudinal associations between increasing depression symptoms and cognitive decline (over a relatively long follow-up duration - LASA study), as well as by the bidirectional prospective associations between depression symptoms and cognitive functioning (over a relatively short follow-up duration - 10/66 study). Whether depression co-occurs, precedes, follows, or accompanies cognitive decline may

depend on the specific depression symptoms experienced and on the follow-up duration over which depression and cognition are assessed. Over a relatively long follow-up duration, the increase in somatic symptoms may be related to a more accelerated course of cognitive decline (perhaps reflecting common neurodegenerative processes), whereas memory dysfunctions may be followed by an increase in depressed affect symptoms (perhaps reflecting a psychological reaction to perceived memory loss). Over a short follow-up duration (10/66 study) depression symptom dimensions show similar bidirectional prospective associations with most cognitive dysfunctions. Taken together my findings suggest that depression accompanies cognitive decline in close temporal proximity.

In closing, my thesis advances current knowledge on the role of educational attainment in accounting for cohort differences in late-life cognitive functioning. Moreover, my research adds key pieces to the depression-cognitive ageing puzzle, by informing on the direction and timing of the longitudinal associations between depression and cognition, and how these associations may vary as a function of the type of depression symptoms experienced. There remains a need for studies using a life course approach to healthy ageing to help clarify the role of experiences such as educational attainment and depression symptoms to cognitive inequalities in late life. Adopting a multidimensional symptom approach to depression could help reach a better understanding of the pathways that link depression to persistent cognitive dysfunctions in old age. Examining underlying factors of late-life cognitive inequalities across birth cohorts could help determine whether cohorts reaching older age in our present day society are cognitively healthier than earlier born cohorts, and what factors may account for these cohort effects. Cognitive decline is one of the

most feared and costly aspects of getting older (Deary et al., 2009). Given the individual and societal costs of population ageing, determining the factors that can help optimise cognitive health in late life and the extent to which increasing life-expectancy is matched by increasing health gains remains a major goal for research and public health.

8.6 References

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